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(54) Title: SUBSTITUTED NITROGEN AND SULFUR ALICYCLIC COMPOUNDS, INCLUDING METHODS FOR SYNTHESIS THEREOF

(57) Abstract

The present invention provides new methods for preparation of various compounds that comprise alicyclic groups with nitrogen or sulfur as ring members, including 2,5-disubstituted tetrahydrothiophenes, 2,5-disubstituted pyrrolidines, 2,6-disubstituted thianes, 2,6-disubstituted hexahydropyridines, 2,7-disubstituted thiepanes, 2,7-disubstituted hexahydroazepines, 2,8-disubstituted thiocanes and 2,8-disubstituted octahydroazocines. The invention further provides novel compounds and pharmaceutical compositions and therapeutic methods that comprise such compounds and compositions.

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SUBSTITUTED NITROGEN AND SULFUR ALICYCLIC COMPOUNDS, INCLUDING METHODS FOR SYNTHESIS THEREOF

The present application claims the benefit of U.S. provisional application number 60/091,710, filed July 3, 1998, which is incorporated herein by reference in its entirety.

BACKGROUND

1. Field of the Invention

The present invention provides new methods for preparation of various heterocyclic ring compounds (sulfur or nitrogen as alicyclic ring members) including 2,5-disubstituted tetrahydrothiophenes, 2,5-disubstituted pyrrolidines, 2,6-disubstituted thianes, 2,6-disubstituted hexahydropyridines, 2,7-disubstituted thiepanes, 2,7-disubstituted hexahydroazepines, 2,8-disubstituted thiocanes and 2,8-disubstituted octahydroazocines. The invention further provides novel compounds and pharmaceutical compositions and therapeutic methods that comprise such compounds.

2. Background

Leukotrienes are recognized potent local mediators, playing a significant role in inflammatory and allegeric responses, including arthritis, asthma, psoriasis and thrombotic disease. Leukotrienes are produced by the oxidation of arachidonic acid by lipoxygenase. More particularly, arachidonic acid is oxidized by 5-lipooxygenase to the hydroperoxide, 5-hydroperoxy-eicosatetraenoic acid (5-HPETE), that is converted to leukotriene A_4, that in turn can be converted to leukotriene B_4, C_4, or D_4. The slow-reacting substance of anaphylaxis is now known to be a mixture of leukotrienes C_4, D_4 and E_4, all of which are potent bronchoconstrictors.

Efforts have been made to identify receptor antagonists or inhibitors of leukotriene biosynthesis, to prevent or minimize pathogenic inflammatory responses

mediated by leukotrienes. For example, European Patent Application Nos. 901171171.0 and 901170171.0 report indole, benzofuran, and benzothiophene lipoxygenase inhibiting compounds. Various 2,5-disubstituted tetrahydrothiophenes and pyrrolidines have exhibited significant biological activity, including as lipoxygenase inhibitors. See U.S. Patent Nos. 5,703,093; 5,681,966; 5,648,486; 5,434,151; and 5,358,938.

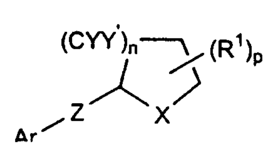
While such compounds can be useful therapeutic agents, current methods for synthesis of at least some of the compounds require lengthy routes, and reagents and protocols that are less preferred in larger scale operations, such as to produce kilogram quantities.

It thus would be desirable to have improved methods to prepare tetrahydrothiophenes and pyrrolidines, particularly new syntheses that facilitate larger scale production of such compounds.

SUMMARY OF THE INVENTION

We have now found new methods for preparation of cyclic sulfur compounds including 2,5-disubstituted tetrahydrothiophenes, 2,6-disubstituted thianes, 2,7-disubstituted thiepanes, and 2,7-disubstituted thiocanes. We also have found new methods for preparation of cyclic nitrogen compounds including 2,5-disubstituted pyrrolidines, 2,6-disubstituted hexahydropyridine, 2,7-disubstituted hexahydroazepine and 2,8-disubstituted octahydroazocine. These methods utilize reagents and synthetic protocols that facilitate large scale manufacture, and provide increased yields relative to prior approaches.

The methods of the invention are suitable for preparation of a variety of cyclic nitrogen or sulfur-containing compounds (i.e., alicyclic compounds having a nitrogen or sulfur ring member), including compounds of the following Formula I:



I

wherein X is S, S(O), $S(O)_2$, N or substituted N (including N-alkyl and N-oxide);

Ar is optionally substituted carbocyclic aryl or optionally substituted heteroaryl;

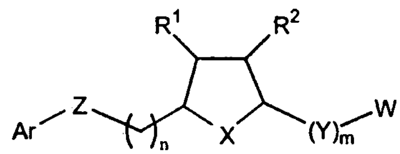
each R^1, Y and Y' is independently hydrogen or a non-hydrogen substituent such as halogen, hydroxyl, optionally substituted alkyl preferably having from 1 to about 20 carbon atoms, optionally substituted alkenyl preferably having from 2 to about 20 carbon atoms, optionally substituted alkynyl preferably having from 2 to about 20 carbon atoms, optionally substituted alkoxy preferably having from 1 to about 20 carbon atoms, optionally substituted alkylthio preferably having from 1 to about 20 carbon atoms, optionally substituted alkylsulfinyl preferably having from 1 to about 20 carbon atoms, optionally substituted alkylsulfonyl preferably having from 1 to about 20 carbon atoms, optionally substituted aminoalkyl preferably having from 1 to about 20 carbon atoms, optionally substituted alkanoyl preferably having from 1 to about 20 carbon atoms, optionally substituted carbocyclic aryl having at least about 6 ring carbons, or substituted or unsubstituted aralkyl having at least about 6 ring carbons, and the like;

Z is a chemical bond, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, or a hetero atom such as O, S, S(O), $S(O)_2$, or NR^1 wherein R^1 is the same as defined immediately above;

n is an integer from 1 to 11, and preferably is 1 to 9, more preferably 1 to 7;

p is an integer from 0 (where the α and β ring positions are fully hydrogen-substituted) to 4; and pharmaceutically acceptable salts thereof.

The methods of the invention are particularly suitable for synthesis of substituted 5-membered ring heterocycles, including compounds of the following Formula II:



II

wherein Ar and X are each the same as defined in Formula I above;

m is 0 or 1; n is 1-6;

W is -AN(OM)C(O)N(R^3)R^4, -N(OM)C(O)N(R^3)R^4, -AN(R^3)C(O)N(OM)R^4, -N(R^3)C(O)N(OM)R^4, -AN(OM)C(O)R^4, -N(OM)C(O)R^4, -AC(O)N(OM)R^4, -C(O)N(OM)R^4, or –C(O)NHA; and A is lower alkyl, lower alkenyl, lower alkynyl, alkylaryl or arylalkyl, wherein one or more carbons optionally can be replaced by N, O or S, however -Y-A-, -A-, or -AW- should not include two adjacent heteroatoms;

M is hydrogen, a pharmaceutically acceptable cation or a metabolically cleavable leaving group;

Y is O, S, S(O), $S(O)_2$, NR^3 or CHR^5;

Z is O, S, S(O), $S(O)_2$, or NR^3;

R^1 and R^2 are each independently hydrogen, lower alkyl, C_{3-8} cycloalkyl, halolower alkyl, halo or -COOH;

R^3 and R^4 are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, C_{1-6}alkoxy-C_{1-10}alkyl, C_{1-6} alkylthio-C_{1-10} alkyl, heteroaryl, or heteroarylalkyl;

R^5 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, arylalkyl, alkaryl, -AN(OM)C(O)N(R^3)R^4, -AN(R^3)C(O)N(OM)R^4, -AN(OM)C(O)R^4, -AC(O)N(OM)R^4, -AS$(O)_x R^3$, -AS$(O)_x CH_2C(O)R^3$, -AS$(O)_x CH_2CH(OH)R^3$, or –AC(O)NHR^3, wherein x is 0-2; and pharmaceutically acceptable of such compounds.

Preferred compounds of Formula II include compounds where Ar is substituted by halo (including but not limited to fluoro), lower alkoxy (including methoxy), lower aryloxy (including phenoxy), W (as defined above in Formula II), cyano, or R^3 (as

defined above in Formula II). Those substituents are also preferred Ar group substituents for compounds of other formulae disclosed herein. Specifically suitable Ar groups for the above Formula II as well as the other formulae disclosed herein include phenyl, trimethoxyphenyl, dimethoxyphenyl, fluorophenyl (specifically 4-fluorophenyl), difluorophenyl, pyridyl, dimethoxypyridyl, quinolinyl, furyl, imidazolyl, and thienyl. Additionally, in Formula II as well as other formulae disclosed herein, W suitably is lower alkyl, such as a branched alkyl group, e.g. $-(CH_2)_nC(alkyl)H-$, wherein n is 1-5, and specifically $-(CH_2)_2C(CH_3)H-$, or lower alkynyl such as of the formula $-C{\equiv}C-CH(alkyl)-$, including $-C{\equiv}C-CH(CH_3)-$.

In some instances, particularly for therapeutic applications, a selected stereoisomer of a compound of the above formulae may be preferred. Accordingly, methods of the invention include preparation of enantiomerically enriched compounds of Formula I.

In a first aspect, synthetic methods of the invention provide thio ring compounds and comprise reaction of an epoxyether substituted aryl compound with a thiolating reagent to form a thioepoxy ether. (As used herein, the term "aryl" as used herein refers to both carbocyclic aryl and hetoaromatic or heteroaryl groups, which terms in turn are further discussed below.) That thioepoxy ether is then reacted with an active methylene compound to form a thiolactone, preferably a γ-thiolactone. The active methylene compound can be a variety of agents. Diethyl and dimethyl malonate are generally preferred, which provide an ethyl or methyl ester as a thiolactone ring substituent. That ester group is then removed (particularly by hydrolysis and decarboxylation), and the lactone suitably reduced to a hydroxy(thioalicyclic)-aryl ether compound, particularly a hydroxy(tetrahydrothiophene)-aryl ether.

The hydroxy(tetrahydrothiophene)-aryl ether compound can be further functionalized as desired, particularly by activating the hydroxyl substituent of the

tetrahydrothiophene followed by substitution of the corresponding position of the thioalicyclic ring such as by a 1-alkyne reagent. Also, rather than directly activating the hydroxyl moiety, that group can be replaced with a halide, and the halide-substituted tetrahydrothiophene reacted with a benzylsulfonic acid reagent.

It also has been found that methods of the invention enable such substitution of the tetrahydrothiophene to proceed with extremely high stereospecificity, e.g. at least greater than about 60 mole percent of one stereoisomer than the other, more typically greater than about 70 or 75 mole percent of one stereoisomer than the other isomer. Recrystallization of the produced enantiomerically enriched mixture has provided very high optical purities, e.g. about 95 mole %, 97 mole % or even 99 mole % or more of the single stereoisomer.

In a further aspect, synthetic methods of the invention provide nitrogen ring compounds and preferably comprise reaction of a sulfonyl substituted hydroxyalkylaryl ether compound, in which the sulfonyl group is enantiomerically enhanced, either in the R or S configuration, with a reagent that will displace the sulfonyl with an azido group with inversion of configuration to form an azidohydroxyaryl ether. That azidohydroxy aryl ether is then oxidized to a 2,3-epoxide, preferably an optically active epoxide such as a (2S,3S) epoxide. That azidohydroxyaryl ether is further reacted with base and then triphenylphosphine to form a pyrrolidine compound which is further reacted to achieve carbon chain extension to yield an alkynylhydroxy arylether substituted pyrrolidine. The hydroxy pyrrolidine can be further functionalized as desired.

These methods surprisingly can proceed as a single step without isolation of intermediates to provide nitrogen ring compounds that have varying ring size as desired. These methods are suitable for preparation of nitrogen ring compounds having from 5 to 12 or more ring members, and are particularly useful for synthesis of nitrogen ring compounds having from 5 to 8 or 9 ring members.

More particularly, larger ring alkynyl-substituted compounds are readily provided through corresponding chain homologation of the epoxy reagent, i.e. by interposing additional "spacing" or alkylene chain members between the reagent's activated positions.

Thus, for example, to prepare an alkynyl-substituted tetrahydopyridine, a reagent is employed that has at least a seven-carbon alkyl or alkylene chain that is activated at the 1- and 7- carbon positions e.g. by substitution by suitable leaving groups (such as those mentioned above), and the 2- and 3- positions of the chain form an epoxide ring. That compound is reacted with base to provide an alkynyl-substituted tetrahydropyridene.

Similarly, to prepare an alkynyl-substituted hexahydroazepine, a reagent is employed that has at least a seven-carbon alkyl or alkylene chain activated (particularly by leaving groups) at the 1- and 8-carbon positions, and the 2- and 3-postion of the chain form an epoxide ring. To prepare an alkynyl-substituted octahydroazocines compound, a reagent is employed that has at least eight-carbon alkyl of alkylene chain activated at the 1- and 9-carbon positions, with the 2- and 3-positions of the chain forming an epoxide ring. Treatment of those respective reagents with appropriate base provides alkynyl-substituted hexahydroazepine and octahydroazocines compound.

In a yet further aspect of the invention, preparative methods are provided that include multiple reactions that surprisingly can proceed as a single step without isolation of intermediates to provide sulfur ring compounds that have varying ring size as desired. These methods are suitable for preparation of sulfur ring compounds having from 5 to 12 or more ring members, and are particularly useful for synthesis of sulfur ring compounds having from 5 to 8 or 9 ring members.

Moreover, it has been surprisingly found that the one step procedure is enantioselective. Hence, if the starting reagent (a 2,3-thioepoxide) is optically active, the resulting substituted thio-ring compound also will be optically active.

More particularly, in this aspect of the invention the methods include formation, in a single step, of an alkynyl-substituted thio-ring compound. For preparation of an alkynyl-tetrahydrothiophene, a compound is reacted that has at least a six-carbon alkyl or alklyene chain that is activated at the 1- and 6-carbon positions such as by substitution by suitable leaving groups, and 2- and 3-carbon positions of the chain form a thioepoxide ring. The leaving groups of the 1- and 6-positions may be e.g. halo, such as chloro or bromo, or an ester, such as an alkyl or aryl sulfonic ester. Preferably, the 1-position is halo-substituted, particularly bromo-, iodo- or chloro-substituted, and the 6-position is substituted by an ester such as by a benzylsulfonyl group. That compound is reacted with a molar excess of a strong base such as an alkyllithium reagent that affords an alkynyl-substituted tetrahydrothiophene in a single step.

Larger ring alkynyl-substituted thio-ring compounds are readily provided through corresponding chain homologation of the thioepoxy reagent, i.e. by interposing additional "spacing" or alkylene chain members between the reagent's activated positions.

Thus, for example, to prepare an alkynyl-substituted thiane, a reagent is employed that has at least a seven-carbon alkyl or alkylene chain that is activated at the 1- and 7-carbon positions e.g. by substitution by suitable leaving groups (such as those mentioned above), and the 2- and 3- positions of the chain form a thioepoxide ring. That compound is reacted with base to provide an alkynyl-substituted thiane.

Similarly, to prepare an alkynyl-substituted thiepane, a reagent is employed that has at least a seven-carbon alkyl or alkylene chain activated (particularly by leaving groups) at the 1- and 8-carbon positions, and the 2- and 3-postion of the chain form a

thioepoxide ring. To prepare an alkynyl-substituted thiocane compound, a reagent is employed that has at least eight-carbon alkyl of alkylene chain activated at the 1- and 9-carbon positions, with the 2- and 3-positions of the chain forming a thioepoxide ring. Treatment of those respective reagents with appropriate base provides alkynyl-substituted thiane and thiocane compounds.

The invention further provides additional methods for synthesis of nitrogen ring compounds, which do not require use of an azide reagent. These methods include cyclization to provide a nitrogen ring compound, preferably having one or more activated positions in the ring to facilitate functionalization of the formed heterocycle. For example, a ring carbon can have a carbonyl group as a direct ring member, or as a pendant group (e.g. pyrrolidinone, and/or pyrrolidinone with an acyl or other alkanoyl ring substituent), hydroxyl, haloalkyl as a pendant group, and the like.

Further provided are new routes to substituted hydroxy ureas. In preferred aspects, these routes include reaction of a protected hydroxyurea (e.g., a compound of the formula $NH_2C(O)NHOR$, where R is a hydroxy protecting group such as *para*-methoxybenzyl-) with a substituted alcohol, preferably in the presence of suitable dehydrating agent(s) to provide an amino ester, which is treated with ammonia and a Lewis acid to provide a hydroxy urea.

As mentioned above, compounds produced by the methods of the invention will be useful as pharmaceutical agents, including to treat disorders or diseases mediated by 5-lipoxygenase such as immune, allegeric and cardiovascular disorders and diseases, e.g. general inflammation, hypertension, skeletal-muscular disorders, osteoarthritis, gout, asthma, lung edema, adult respiratory distress syndrome, pain, aggregation of platelets, shock, rheumatoid arthritis, psoriatic arthritis, psoriasis, autoimmune uveitis, allergic encephalomyelitis, systemic lupus erythematosis, acute necrotizing hemmorrhagic encephalopathy, idiopathic thrombocytopenia, polychondritis, chronic active hepatitis,

idiopathic sprue, Crohn's disease, Graves ophthalmopathy, primary biliary cirrhosis, uveitis posterior, interstitial lung fibrosis, allergic asthma and inappropriate allergic responses to environmental stimuli.

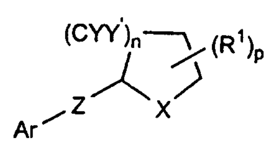
In other aspects, the invention provides new compounds as well as pharmaceutical compositions that comprise one or more of such compounds preferably with a pharmaceutically acceptable carrier. More particularly, compounds of the invention include those of Formula I above, where n is 2 or greater (i.e. compounds with alicyclic rings that have 6 or more ring members), which includes compounds of Formulae III, IIIa, IV, IVa, V, Va, as those formulae are defined below. The invention further provides methods for treatment and/or prophylaxis of various disorders and diseases including those disclosed above such as immune, allegeric and cardiovascular disorders and diseases , the methods in general comprising administering an effective amount of one or more compounds of Formula I above, where n is 2 or greater, to a subject, such as a mammal particularly a primate such as a human, that is suffering from or susceptible to such a disorder or disease.

Compounds produced by the methods of the invention are useful as synthetic intermediates to prepare other compounds that will be useful for therapeutic applications.

Other aspects of the invention are disclosed infra.

DETAILED DESCRIPTION OF THE INVENTION

As discussed above, the invention provides methods that are particularly suitable for synthesis of compounds of the following Formula I:

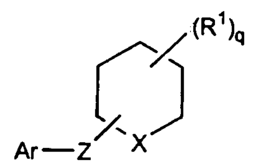


I

wherein Ar, Z, Y, Y', R^1, n and p are as defined above.

As discussed above, preferred compounds that can be produced by the methods of the invention include substituted tetrahydrothiophenes, pyrrolidines, thianes, hexahydropyridines, thiepanes, hexahydroazepines, thiocanes and octahydroazocines.

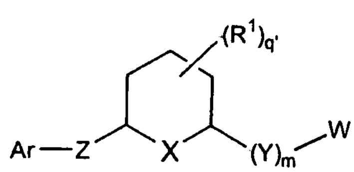
More particularly, preferred compounds produced by the methods of the invention include substituted thianes and hexahydropyridines including substituted thianes and hexahydropyridines of the following Formula III:



III

wherein Ar, X, Z and R^1 are each the same as defined above for Formula I, and q is an integer of from 0 to 9, and preferably q is 1, 2, 3 or 4; and pharmaceutically acceptable salts thereof.

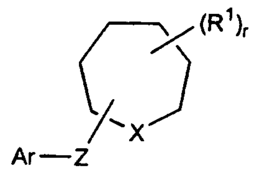
Generally preferred are 2,6-disubstituted thianes and hexahydropyridines, such as compounds of the following Formula IIIa;



IIIa

wherein Ar, X, Z, Y, W, R^1 and m are each the same as defined for Formula II above, and q' is an integer of from 0 to 6 , and preferably q' is 0, 1, 2, 3 or 4; and pharmaceutically acceptable salts thereof.

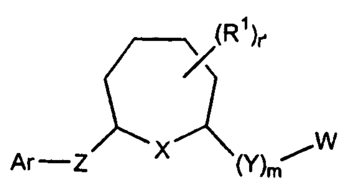
The methods are also particularly useful for preparations of substituted thiepanes and hexahydroazepines including compounds of the following Formula IV:



IV

wherein Ar, X, Z and R^1 are each the same as defined above for Formula I, and r is an integer of from 0 to 11, and preferable r is 1, 2, 3 or 4; and pharmaceutically acceptable salts thereof.

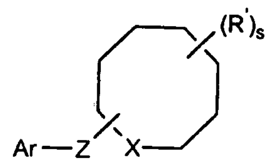
Generally preferred are 2,7-disubstituted thiepanes and hexahydroazepines such as compounds of the following Formula IVa:



IVa

wherein Ar, X, Z, Y, W, R' and m are each the same as defined for Formula II above, and r' is an integer of from 0 to 10, and preferably r' is 0, 1, 2, 3 or 4; and pharmaceutically acceptable salts thereof.

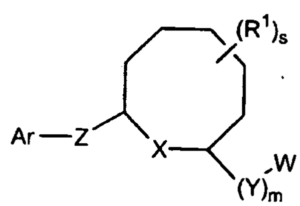
Still further, methods of the invention can be especially useful for synthesis of substituted thiocanes and octahydroazocines, such as compounds of the following Formula V:



V

wherein Ar, X, Z and R' are each the same as defined above for Formula I, and s is an integer of from 0 to 13, and preferable s is 1, 2, 3 or 4; and pharmaceutically acceptable salts thereof.

Generally preferred are 2,8-disubstituted thiocanes and octahydroazocines such as compounds of the following Formula Va:



Va

wherein Ar, X, Z, Y, W, R^1 and m are each the same as defined for Formula II above, and s is an integer of from 0 to 10, and preferably s is 0, 1, 2, 3 or 4; and pharmaceutically acceptable salts thereof.

The term alkyl, as used herein, unless otherwise specified, refers to a saturated straight, branched, or cyclic hydrocarbon preferably of C_1 to C_{10}, and specifically includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, 3-methylpentyl, 2,2-dimethylbutyl, and

2,3-dimethylbutyl. The alkyl group can be optionally substituted with any appropriate group, including but not limited to R^3 or one or more moieties selected from the group consisting of halo, hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as disclosed in Greene et al., "Protective Groups in Organic Synthesis", John Wiley and Sons, Second Edition, 1991.

The term halo, as used herein, refers to chloro, fluoro, iodo, or bromo.

The term lower alkyl, as used herein, and unless otherwise specified, refers to a C_1 to C_6 saturated straight, branched, or cyclic (in the case of C_{5-6}) hydrocarbon, and specifically includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl, optionally substituted as described above for the alkyl groups.

The term alkenyl, as referred to herein, and unless otherwise specified, refers to a straight, branched, or cyclic (in the case of C_{5-6}) hydrocarbon preferably of C_2 to C_{10} with at least one double bond, optionally substituted as described above.

The term lower alkenyl, as referred to herein, and unless otherwise specified, refers to an alkenyl group of C_2 to C_6, and specifically includes vinyl and allyl.

The term lower alkylamino refers to an amino group that has one or two lower alkyl substituents.

The term alkynyl, as referred to herein, and unless otherwise specified, refers to preferably C_2 to C_{10} straight or branched hydrocarbon with at least one triple bond,

optionally substituted as described above. The term lower alkynyl, as referred to herein, and unless otherwise specified, refers to a C_2 to C_6 alkynyl group, specifically including acetylenyl, propynyl, and -C≡C-CH(alkyl)-, including -C≡C-CH(CH_3)-.

The term carbocyclic aryl, as used herein, and unless otherwise specified, refers to non-hetero aromatic groups that have 1 to 3 separate or fused rings and 6 to about 18 carbon ring atoms and include e.g. phenyl, napthyl, biphenyl, phenanthryl, anthracyl, and the like. The carbocyclic aryl group can be optionally substituted with any suitable group, including but not limited to one or moieties selected from the group consisting of halo, hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene et al., "Protective Groups in Organic Synthesis", John Wiley and Sons, Second Edition, 1991, and preferably with halo (including but not limited to fluoro), lower alkoxy (including methoxy), lower aryloxy (including phenoxy), W, cyano, or R^3.

The term haloalkyl, haloalkenyl, or haloalkynyl refers to alkyl, alkenyl, or alkynyl group in which at least one of the hydrogens in the group has been replaced with a halogen atom.

The term heteroaryl, heterocycle or heteroaromatic, as used herein, refers to an aromatic moiety that includes at least one sulfur, oxygen, or nitrogen in the aromatic ring, which can optionally be substituted as described above for the aryl groups. Non-limiting examples are pyrryl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuran, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl. Suitable heteroaromatic or heteroaryl groups will have 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero atoms (N, O or S).

The term arylalkyl refers to a carbocyclic aryl group with an alkyl substituent.

The term alkylaryl refers to an alkyl group that has a carbocyclic aryl substituent.

The term organic or inorganic anion refers to an organic or inorganic moiety that carries a negative charge and can be used as the negative portion of a salt.

The term "pharmaceutically acceptable cation" refers to an organic or inorganic moiety that carries a positive charge and that can be administered in association with a pharmaceutical agent, for example, as a counter cation in a salt. Pharmaceutically acceptable cations are known to those of skill in the art, and include but are not limited to sodium, potassium, and quaternary amine.

The term "metabolically cleavable leaving group" refers to a moiety that can be cleaved in vivo from the molecule to which it is attached, and includes but it not limited to an organic or inorganic anion, a pharmaceutically acceptable cation, acryl (for example (alkyl)C(O), including acetyl, propionyl, and butyryl), alkyl, phosphate, sulfate and sulfonate.

Alkylene and heteroalkylene groups typically will have about 1 to about 8 atoms in the chain, more typically 1 to about 6 atoms in the linkage. Alkenylene, heteroalkenylene, alkynylene and heteroalkynylene groups typically will have about 2 to about 8 atoms in the chain, more typically 2 to about 6 atoms in the linkage, and one or more unsaturated carbon-carbon bonds, typically one or two unsaturated carbon-carbon bonds. A heteroalkylene, heteroalkenylene or heteroalkynylene group will have at least one hetero atom (N, O or S) as a divalent chain member.

The term alkanoyl refers to groups that in general formulae generally will have from 1 to about 16 carbon atoms and at least one carbonyl (C=O) moiety, more typically

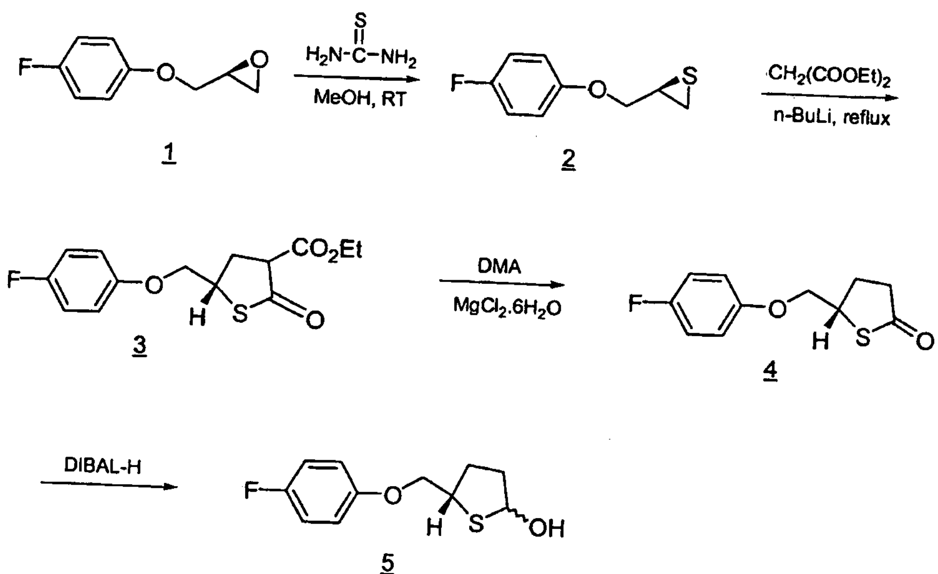
from 1 to about 8 carbon atoms, still more typically 1 to about 4-6 carbon atoms. The term alkylthio generally refers to moieties having one or more thioether linkages and preferably from 1 to about 12 carbon atoms, more preferably from 1 to about 6 carbon atoms. The term alkylsulfinyl generally refers to moieties having one or more sulfinyl (S(O)) linkages and preferably from 1 to about 12 carbon atoms, more preferably from 1 to about 6 carbon atoms. The term alkylsulfonyl generally refers to moieties having one or more sulfonyl ($S(O)_2$) linkages and preferably from 1 to about 12 carbon atoms, more preferably from 1 to about 6 carbon atoms. The term aminoalkyl generally refers to groups having one or more N atoms and from 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms.

As discussed above, various substituent groups of the above formulae may be optionally substituted. Suitable groups that may be present on such a "substituted" group include e.g. halogen such as fluoro, chloro, bromo and iodo; cyano; hydroxyl; nitro; azido; sulfhydryl; alkanoyl e.g. C_{1-6} alkanoyl group such as acetyl and the like; carboxamido; alkyl groups including those groups having 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms; alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon atoms, preferably from 2 to about 6 carbon atoms; alkoxy groups having one or more oxygen linkages and from 1 to about 12 carbon atoms, preferably 1 to about 6 carbon atoms; aryloxy such as phenoxy; alkylthio groups including those moieties having one or more thioether linkages and from 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms; alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms; alkylsulfonyl groups including those moieties having one or more sulfonyl linkages and from 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms; aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms; carbocyclic aryl having 6 or more carbons, particularly phenyl; aryloxy such as phenoxy; aralkyl having 1 to 3 separate or fused

rings and from 6 to about 18 carbon ring atoms, with benzyl being a preferred group; aralkoxy having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, with O-benzyl being a preferred group; or a heteroaromatic or heteroalicyclic group having 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N, O or S atoms, e.g. coumarinyl, quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, benzofuranyl, benzothiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolidinyl. A "substituted" group of a compound of the invention prepared by a method of the invention may be substituted at one or more available positions, typically 1 to about 3 positions, by one or more suitable groups such as those listed immediately above.

Particularly preferred preparative methods of the invention are exemplified in the following Schemes I through IV. For purposes of exemplification only, particularly preferred compounds and substituents are depicted in the Schemes, and it will be understood that a variety of other compounds can be employed in a similar manner as described below with respect to the exemplified compounds. For instance, the carbocyclic aryl group of 4-fluorophenol is depicted throughout the Schemes, although a wide variety of other aryl groups could be employed in the same or similar manner as fluorophenyl. It should also be understood that references to "aryl" with respect to the Schemes includes those groups specified for the substituent Ar in Formula I above and thus encompasses carbocyclic aryl such as phenyl and the like as well as heteroaryl groups. Additionally while compounds in the below Scheme generally depict substitution at the ring carbons α to the ring hetero atom, other ring positions can be readily substituted e.g. by using appropriately substituted starting reagents. Also, while various stereoisomers are depicted in the below Schemes, corresponding other stereoisomers can be readily obtained by use of the corresponding optically active reagents or enantiomertic selective reactions or separations.

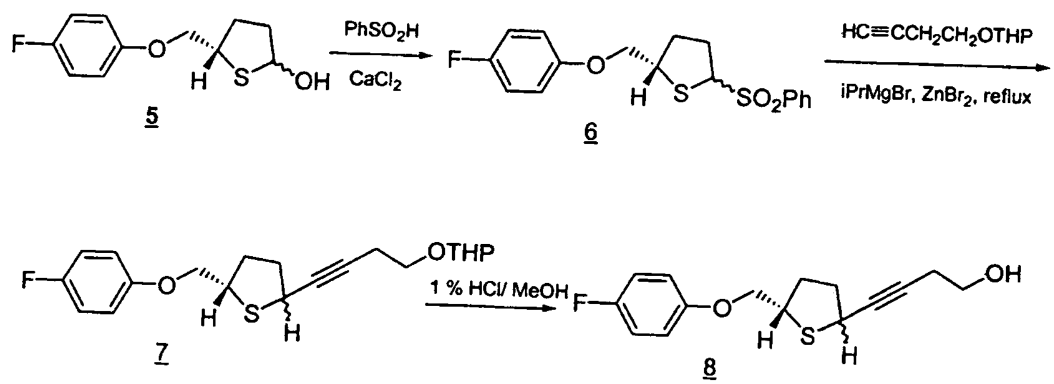
Scheme I



Scheme I exemplifies a preferred preparative method of the invention wherein the enantiomerically pure epoxide 1 and thiourea react to form the cyclic sulfide (thiirane) 2 maintaining the R configuration. Preferred epoxides are those that are enantiomerically enriched with *R* stereochemistry at the C2 carbon, such as the (*R*) glycidyl fluorophenyl 1 shown above. The preferred epoxide 1 and thiourea are reacted in a suitable solvent such as methanol for a time and temperature sufficient for reaction completion to provide thioaryl ether 2. See Example 1, Part 1 below for exemplary reaction conditions. The compound 1 and thiourea typically react in a suitable solvent, e.g. methanol, ethanol and the like. Enantiomerically enriched epoxides suitable for conversion to a suitable (*R*) thioglycidyl ether are commercially available or can be readily prepared by known procedures. See, for instance, U.S. Patents Nos. 4,946,974 and 5,332,843 to Sharpless et al. for preparation of optically active derivatives of glycidol.

The thioepoxyaryl ether 2 then is reacted with an active methylene group, such as a diethyl or dimethyl malonate to provide thiobutyrolactone 3. The exocyclic ester of 3 is then suitably cleaved, e.g. with reaction with magnesium chloride hexahydrate, to provide the corresponding carbonyl thiolactone ether 4. See Example 1, Part 3 which follows for an exemplary reaction conditions. The thiolactone 4 is then reduced to the hydroxy-tetrahydrothiophene 5. Suitable reducing agents include e.g. DIBAL-H and the like. See Example 1, Part 4, which follows.

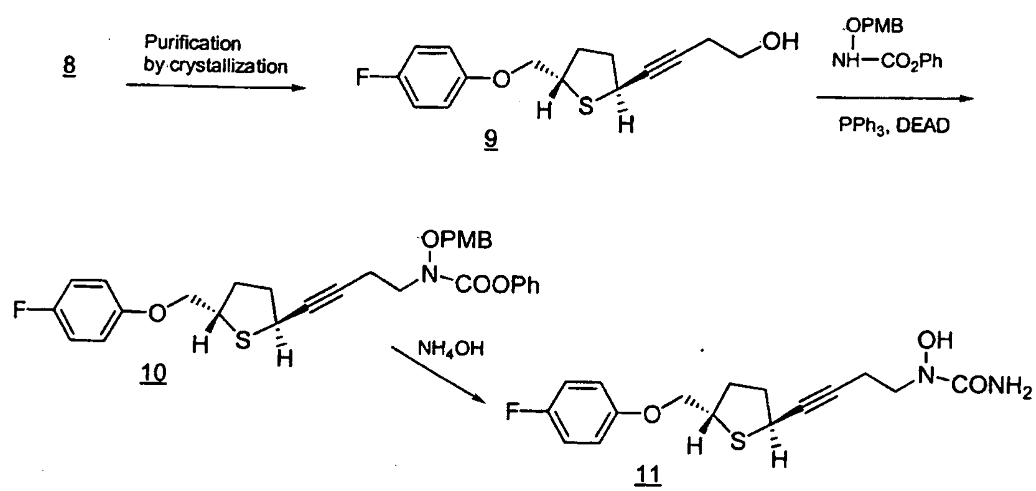
Scheme II



Schemes II and III below exemplify further preferred methods of the invention for synthesis of alkynyl-substituted tetrahydrothiophene ethers. More specifically, the hydroxy substituent of tetrahydrothiophene 5 is preferably activated, e.g. as an ether, tosyl, mesyl or benzene sulfinic acid derivative. Thus, as depicted in Scheme II, the hydroxy moiety of 5 can be reacted with a suitable sulfinic or silyl reagent, e.g. to form the benzenesulfonyl derivative 6, or with reagents for silylation, e.g. a silyl chloride such as TMSCl. See Example 1, Part 5 and Example 2, Part 1 for suitable reaction conditions.

The activated aryltetrahydrothiophene ether 6 can then react to provide the alkynyl-substituted tetrahydrothiophene 7 by treatment with a 1-alkyne in the presence of a strong base such an alkyllithium. Preferably the alkyne reagent contains a protected hydroxy moiety such as an ether, e.g. a methoxyethoxymethyl, methoxymethyl or tetrahydropyranyl ether 7 as depicted in the above Scheme. The hydroxy group can be readily deprotected after coupling of the alkynyl reagent to the tetrahydrothiophene ring, e.g. by treatment with dilute acid to yield the corresponding alcohol 8. Typically, the alkyne reagent will contain a primary or secondary hydroxy moiety. See Example 1, Part 7 for suitable reaction conditions.

Scheme III

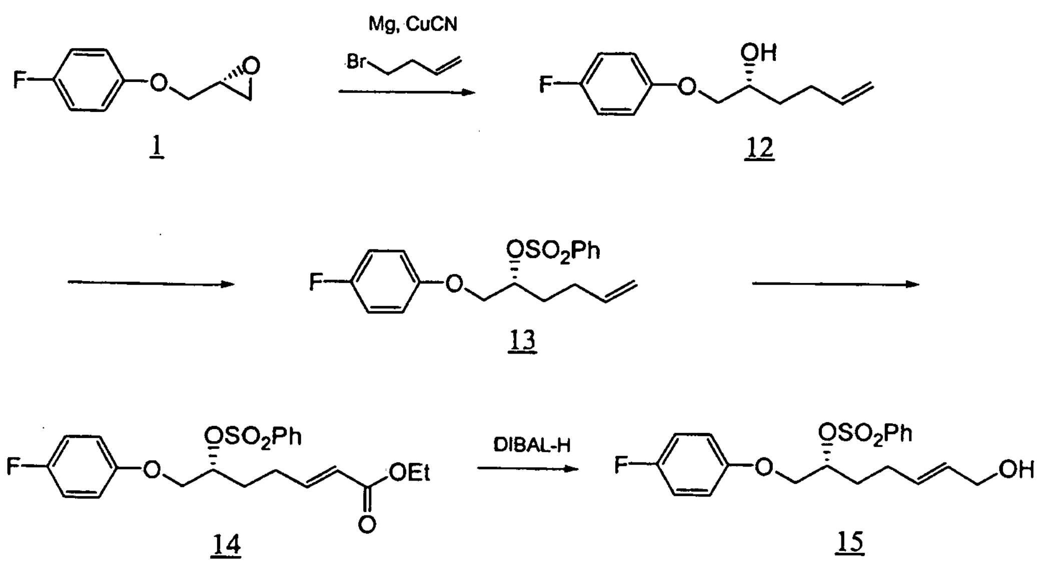


As indicated in Scheme III, the enantiomerically enriched hydroxy-tetrahydrothiophene 9 can be obtained by purification by crystallization of the isomeric mixture 8. The hydroxy tetrahydrothiophene 9 can be further functionalized as desired by amidation using a N,O-substituted hydroxylamine such as N-phenoxycarbonyl-O-*p*-methoxybenzyl-hydroxylamine in the presence of dehydrating reagents such as, triphenylphosphine and diethylazodicarboxylate, followed by treatment of the resulting

intermediate 10 with ammonia to yield the hydroxylamine tetrahydrothiophene 11. See Example 1, Part 9 and Part 10 for optimal reaction conditions.

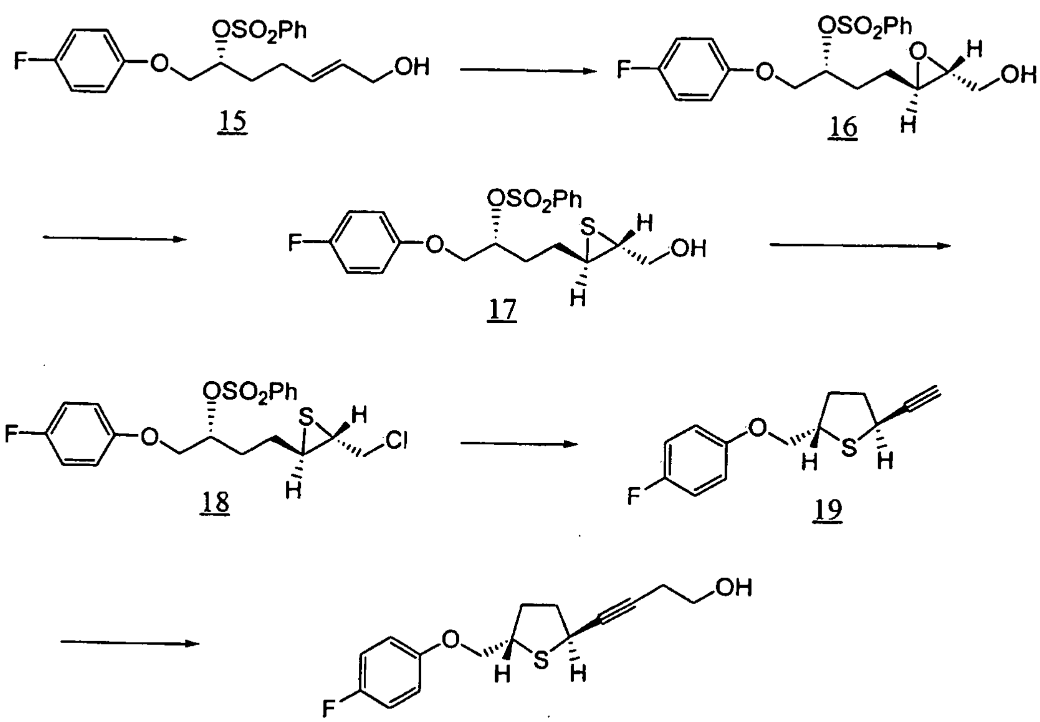
Schemes IV-VI below exemplify a further aspect of the invention that provides methods for synthesis of larger sulfur heterocyclic compounds such as thianes, thiepanes and thiocanes and an alternative method of obtaining substituted tetrahydrothiophenes. This is accomplished by utilizing analogs of compound 15 which have an extended alkyl chain of the appropriate length.

Scheme IV



As shown in scheme IV, intermediate 15 is suitably obtained by reaction of arylepoxy ether 1 and the appropriate haloalkene utilizing Grignard conditions to obtain the alkene 12. Thus, to synthesize homoallylic alcohol 15, the arylepoxy ether 1 and a haloalkene such as 4-bromo-1-butene, react in the presence of magnesium and a suitable catalyst system such as iodine and cuprous cyanide to provide the arylalkene ether 12. The secondary hydroxyl group of 12 is suitably protected, e.g. preferably as a sulfonic ester to provide the terminal alkene 13. Alkene 13 is further extended and fuctionalized by condensation to form the α,β-unsaturated ester 14. The ester 14 is then reduced to an alcohol, typically by treatment with a strong base such as DIBAL-H to obtain intermediate homo allylic alcohol 15.

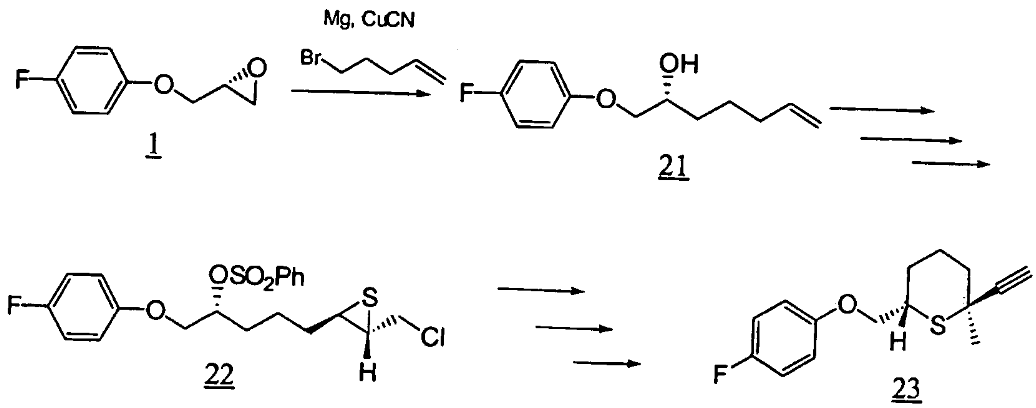
Scheme V



As shown in Scheme V, the homoallylic alcohol 15 is then enantioselectively oxidized to provide the epoxy group of 16. Scheme V shows the Sharpless asymmetric epoxidation of 15 to give the corresponding (2S,3S, 6S) arylether epoxide 16. Other procedures may be used where in an optically active ligand or catalyst is used to promote enanteoselectivity of the oxidation of 15. The racemic epoxides may also be resolved, e.g. by chromatography using an optically active packing material. The arylether epoxide 16 is then converted to the corresponding thiirane 17 by reaction with thiourea or phosphorous pentoxide. The C1 alcohol of compound 17 is then halogenated to provide the (2S,3S,6S) thiirane 18 where suitable halogens include chlorine and bromine. Scheme V illustrates halogenation by in situ activation of the hydroxyl group to a mesylate e.g. methane sulfonyl chloride with a nitrogen base such as pyridine or triethyl amine and can include catalysis by dimethylaminopyridine. Subsequent substitution may be accomplished using the appropriate lithium salt e.g. lithium chloride or lithium bromide, dissolved in an appropriate solvent such as dimethylformamide or THF. The arylether thiirane 17 could also be directly halogenated using an appropriate reagent.

Dehalogenation with concomitant rearrangement of compound 18 to the (3R) hydroxy alkyne 19 is accomplished by reaction with an appropriate lithium base, such as lithium diisopropyl amine, in a suitable solvent e.g. THF. The alkyne 19 is extended by two carbons units by treatment with butyllithium in the presence of boron trifluoride diethyl etherate followed by ethylene oxide to yield the trans-tetrahydrothiophine 8.

Scheme VI

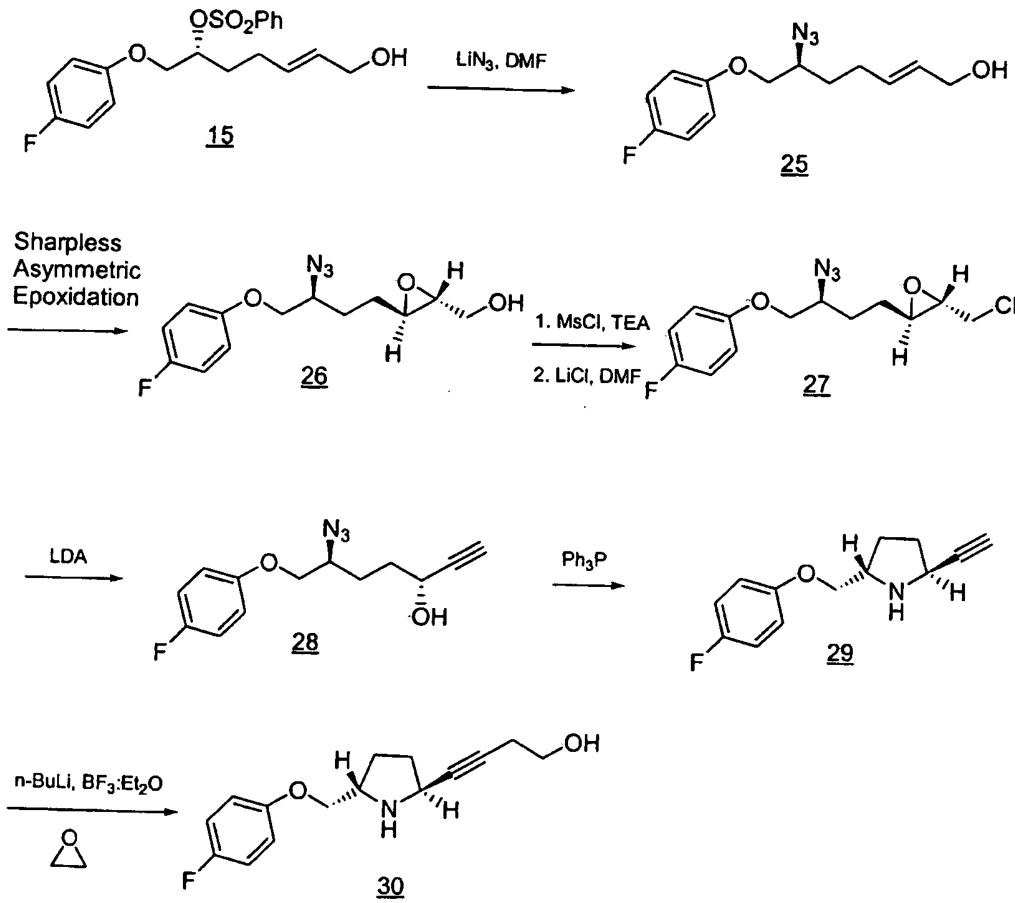


This methodology may be used to synthesize tetrahydrothiophenes by reacting 1 and an appropriate alkene such as 4-bromo-1-butyene to obtain the necessary terminal alkene 12 for synthesis of tetrahydrothiophenes. Similarly preparation of key intermediates of thianes are obtained by reaction of 1 and an appropriate alkene such as 5-bromo-1-pentene, thiepanes by reaction of 1 and an appropriate alkene such as 6-bromo-1-hexene and thiocanes by reaction of 1 and an appropriate alkene such as 7-bromo-1-heptene. The resulting terminal alkenes of each of the above reactions are converted to the appropriate thiirane analogs of 22 and further reacted to obtain the appropriate hydroxyalkynyl-sulfur heterocyclic compounds analogous to 23. The hydroxy alkynyl analogs of 23 are then converted to the appropriate substituted hydroxy ureas by methods described above.

In a further aspect, routes to substituted hydroxy ureas are provided. More particularly, a protected hydroxy urea (e.g., a compound of the formula $NH_2C(O)NHOR$, where R is a hydroxy protecting group such as an alkyl, aryl or preferably aryalkyl ether such as an ether of an optionally substituted (phenyl)OCH_2-) is reacted with a substituted alcohol compound, such as analogues of 9 of Scheme III, preferably in the presence of suitable dehydrating agent(s) such as triphenyl phosphine and diethylazodicarboxylate (DEAD), to provide an amino ester, i.e. a moiety of the formula $-NRC(O)OR^1R$ where R is as defined immediately above and R^1 is a non-hydrogen group such as aryl, particularly phenyl, alkyl, e.g. C_{1-10} alkyl, etc. That amino ester is then treated with ammonia and a Lewis acid such as boron trifluoride etherate and the like to provide a hydroxy urea. In a preferred method of hydroxy urea formation, para-methoxybenzyl- is utilized as the hydroxy protection group R.

In a second preferred aspect, synthetic methods of the invention include preparation of compounds useful as intermediates to prepare pyrrolidine compounds of the above Formula II (X being nitrogen in Formula II).

Scheme VII

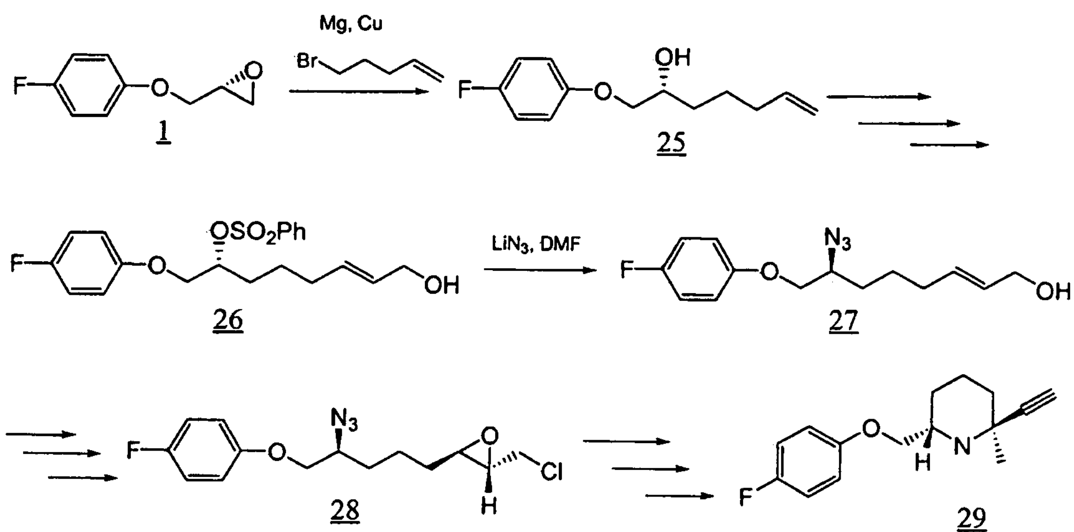


Scheme VII exemplifies a preferred preparative method of the invention wherein the enantiomerically enriched (6R) sufonic ester of the homo allylic alcohol 15 is transformed to an azide 25 with inversion to the S configuration at the C6 carbon. Typically sulfonic ester 15 and a suitable reagent such as lithium azide react in a solvent such as dimethyl formamide to yield the (6S) azide 25 The (6S) azido alcohol 25 is then enantioselectively oxidized to provide the epoxy group of 26. Scheme VII shows the Sharpless asymmetric epoxidation of 25 to give the corresponding (2S,3S, 6S) epoxyazide 26. Other procedures may be used where in an optically active ligand or

catalyst is used to promote enanteoselectivity of the oxidation of 25. The racemic epoxides may also be resolved, e.g. by chromatography using an optically active packing material. The C1 alcohol of compound 26 is then halogenated to provide the (2S,3S,6S)epoxy azide 27 where suitable halogens include chlorine and bromine. Scheme IV illustrates halogenation by in situ activation of the hydroxyl group to a mesylate e.g. methane sulfonyl chloride with a nitrogen base such as pyridine or triethyl amine and can include catalysis by dimethylaminopyridine. Subsequent substitution may be accomplished using the appropriate lithium salt e.g. lithium chloride or lithium bromide, dissolved in an appropriate solvent such as dimethylformamide or THF. The epoxy azide 26 could also be directly halogenated using an appropriate reagent.

Dehalogenation with concomitant rearrangement of compound 27 to the (3R) hydroxy alkyne 28 is accomplished by reaction with an appropriate lithium base, such as lithium diisopropyl amine, in a suitable solvent e.g. THF. The alkyne 28 is reacted with triphenylphosphine in an appropriate manner to yield the trans-alkynyl-pyrrolidine 29. The alkyne 29 is extended by two carbons units by treatment with butyllithium in the presence of boron trifluoride diethyl etherate followed by ethylene oxide to yield the trans-hydroxypyrrolidine 30.

Scheme VIII



1 25 26 27 28 29

As discussed above, in a further aspect the invention provides methods for synthesis of larger nitrogen heterocyclic compounds such as hexahydropyridines, hexahydroazepines, and octahydroazocines. This is accomplished by utilizing reagents akin to compound 15 (Scheme VII) which have an extended alkyl chain of the appropriate length as previously described above and shown in Scheme VIII. The synthesis of hexahydropyridine by way of this method is outlined immediately above in Scheme VIII. Thus, to obtain the homoallylic alcohol 26, the arylepoxy ether 1 and and an appropriate haloalkene such as 5-bromo-1-pentene react in the presence of magnesium and a suitable catalyst system such as iodine and cuprous cyanide to provide the arylalkene ether 25. The secondary hydroxy group is suitably protected. e.g. as an ester, preferrably a sulfonic ester and reacted as described for Scheme VII to obtain homo allylic alcohol 26. This methodology may be used to synthesize pyrrolidines by reacting 1 and an appropriate haloalkene such as 4-bromo-1-butyene to obtain the necessary terminal alkene 12 necessary for synthesis of pyrrolidines. Similarly preparation of key

intermediates of hexahydropyridines are obtained by reaction of 1 and an appropriate haloalkene such as 5-bromo-1-pentene, hexahydroazepines by reaction of 1 and 6-bromo-1-hexene and octahydroazocines by reaction of 1 and an appropriate haloalkene such as 7-bromo-1-heptene. The resulting terminal alkenes of each of the above reaction products are converted to the appropriate homo allylic alcohol analogs of 15 and 25. The homo allylic alcohol can then be processed by methodologies described for Scheme VII to obtain the desired disubstituted nitrogen ring heterocycle.

In the following Schemes IX and X, the compound numerals in the below discussions of those Schemes are made in reference to the compound depicted in the particular Scheme.

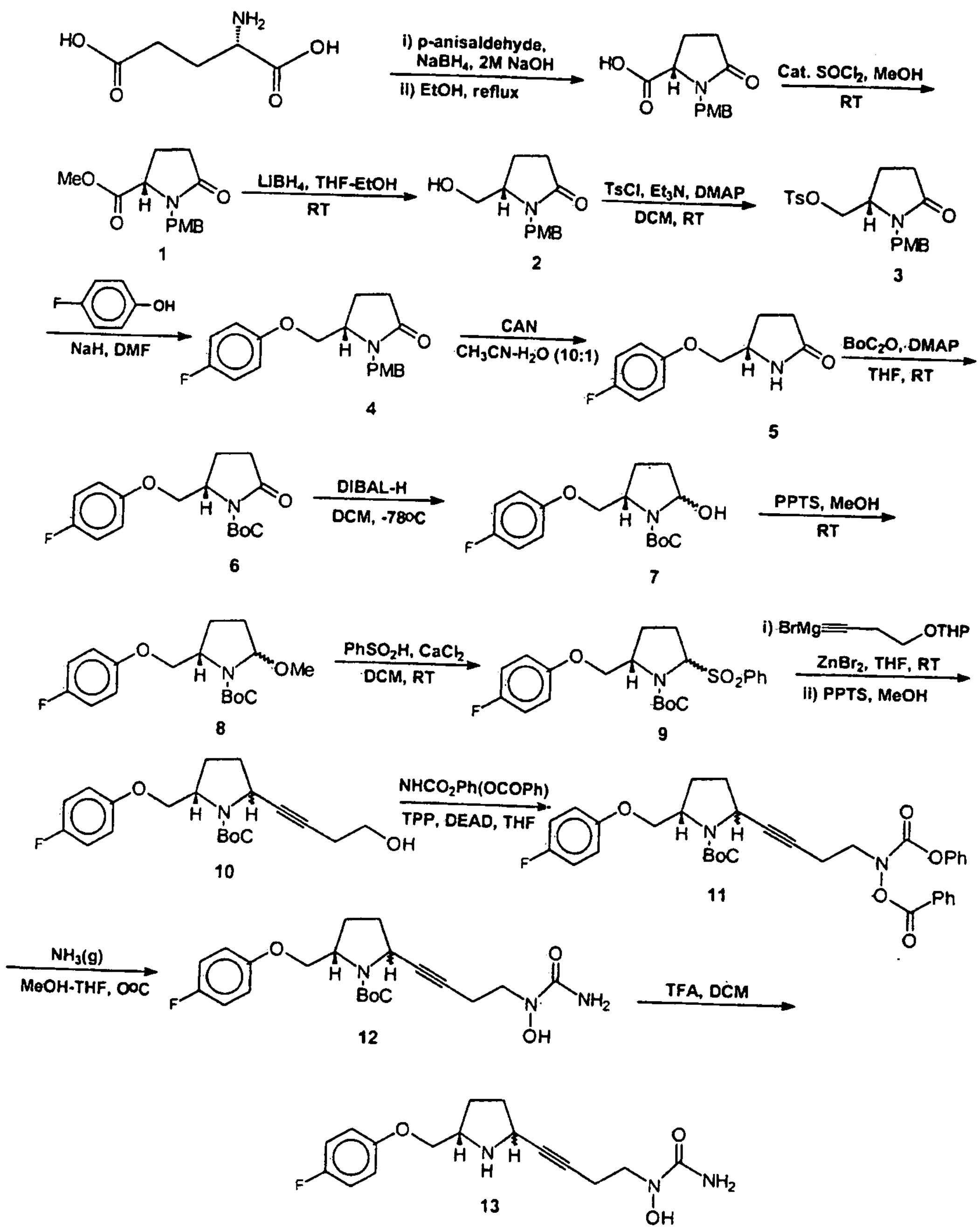
In a further aspect, as generally exemplified in Scheme IX below, the invention includes methods to prepare nitrogen ring compounds of the invention without employing an azide intermediate. Thus, as depicted in Scheme IX below, an amino acid reagent is cyclized to provide a nitrogen ring compound (pyrrolidinone 1), which can be functionalized to provide a desired aryl ring substituent (fluorophenyl as exemplified in Scheme IX). The pyrrolidinone can be reduced, and functionalized as desired, e.g. to form an activated ring carbon by reaction with sulfinic compound, such as an optionally phenyl sulfinic reagent, followed by nucleophilic substitution to that ring carbon, such as to provide alkyne 10 depicted in Scheme IX. See Example 2 below for exemplary preferred reaction conditions. That addition product can be further reacted as desired, including as discussed above to provide a hydroxy urea moiety, i.e. compound 13.

In the Scheme IX, the displacement reaction of compound 3 to compound 4 proceeds with an aryl nucleophile in the presence of a hydride reagent (base), such as potassium hydride or more preferably sodium hydride to yield the alcicylic compound having an arylalkyl substituent, particularly an aryalkoxy substituent as depicted in the Scheme below. Preferred aryl nucelophiles include aryl compounds having one or more

hydroxy ring substituents (i.e. an aryl hydroxy compound), preferably a carboxylic aromatic compound such as an optionally substituted phenol, e.g. phenol optionally substituted by halo, C_{1-6} alkyl, C_{1-6} alkoxy, cyano and the like. The aryl nucelophile is preferably reacted with a nitrogen alicyclic compound having an alkyl ring substituent, typically a C_{1-8} or C_{1-6} alkyl such as methyl and the like that preferably has an activated carbon, e.g. a carbon substituted by a sulfonic ester (e.g. tosylate, mesylate, etc.), where the aryl nucleophile reacts.

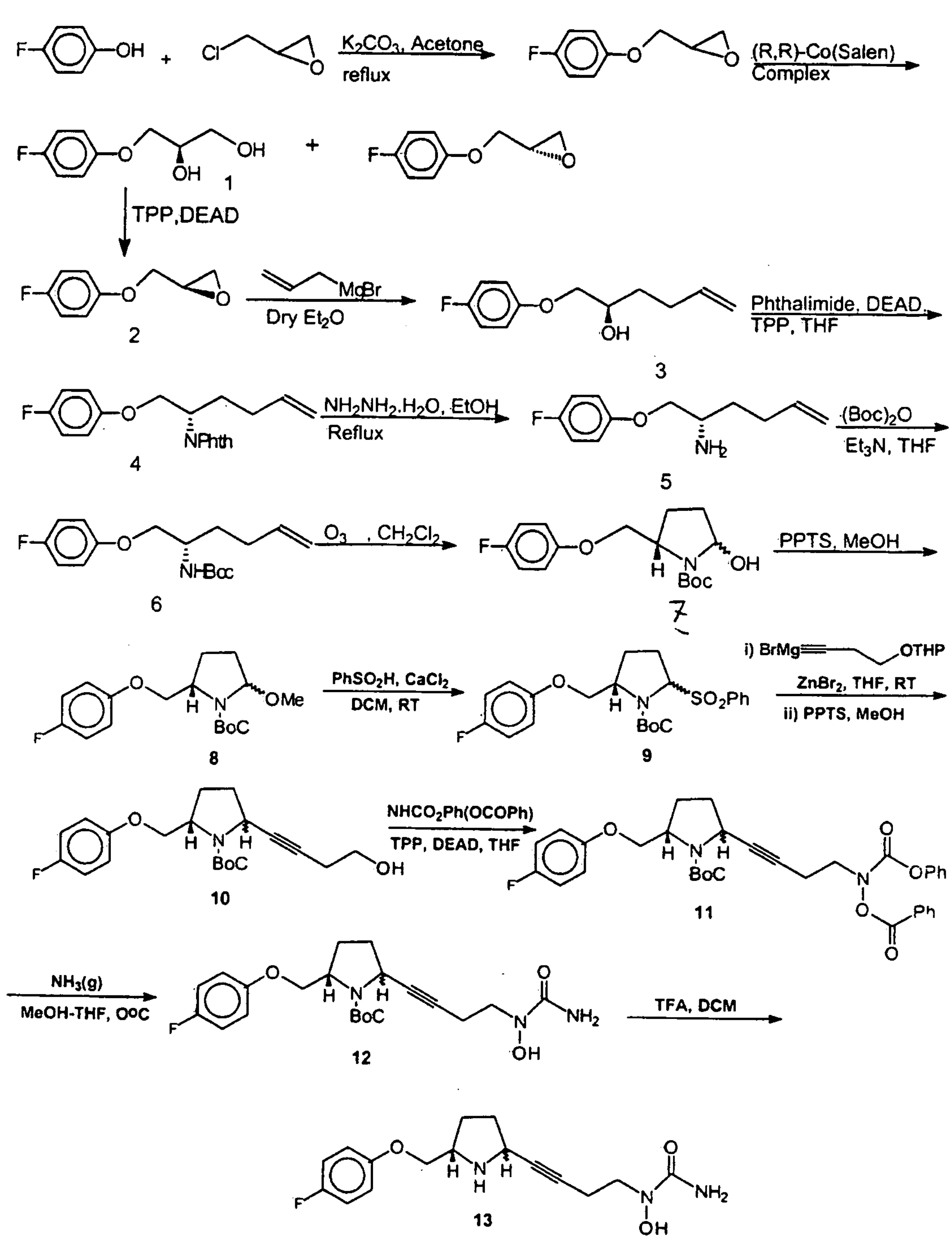
Additionally, the conversion of alicyclic compound having a hydroxy ring substituent to the corresponding sulfinic ester (exemplified as 7 to 9 below) can proceed via an alkoxy intermediate (e.g. C_{1-8} alkoxy, more preferably C_{1-3} alkoxy, more preferably methoxy) intermediate by esterfication of the hydroxy ring moiety e.g. by reaction of the corresponding alcohol such as methanol and the like followed by reaction of alkoxy ring substituent with a sulfinic acid reagent, preferably an aryl reagent such as optionally substituted phenyl sulfinic acid. For example, the phenyl sulfinic acid reagent may be optionally substituted on the phenyl ring by C_{1-8} alkyl preferably methyl, C_{1-8} alkoxy, cyano, halo and the like.

Scheme IX


NH2
HO
OH
i) p-anisaldehyde, NaBH4, 2M NaOH
ii) EtOH, reflux
PMB
Cat. SOCl2, MeOH
RT
MeO
1
LiBH4, THF-EtOH
RT
2
TsCl, Et3N, DMAP
DCM, RT
TsO
3
NaH, DMF
4
CAN
CH3CN-H2O (10:1)
5
BoC2O, DMAP
THF, RT
BoC
6
DIBAL-H
DCM, -78oC
7
PPTS, MeOH
RT
OMe
8
PhSO2H, CaCl2
DCM, RT
SO2Ph
9
i) BrMg OTHP
ZnBr2, THF, RT
ii) PPTS, MeOH
10
NHCO2Ph(OCOPh)
TPP, DEAD, THF
OPh
Ph
11
NH3(g)
MeOH-THF, OoC
NH2
12
TFA, DCM
13

Scheme X below depicts another route to nitrogen ring compounds of the invention without an azide intermediate compound. In this approach, an alcohol, which may be optically active to provide a resolved final product, can be provided by ring-opening of an epoxide (which may be optically active). The alcohol can be substituted be a variety of groups, including aryl groups, as exemplified in the below Scheme X. That alcohol (compound 3 below) then can be functionalized as desired to provide a nitrogen that can be cyclized to provide a nitrogen ring member. Thus, for example, as shown in the below Scheme X, the alcohol intermediate can be reacted with a phthalimide, followed by hydrazine to provide an amine which can be cyclized to provide a nitrogen ring, e.g. by ozonolysis of the terminal alkene to an aldehyde which then cyclizes to 7. The amine group and alkene group can be spaced by additional carbons to provide nitrogen ring groups with additional carbon ring members. Thus, for example, to provide a six-member ring, four (typically saturated) carbons would be positioned between the amine and the alkene; to provide a seven-membered ring, five (typically saturated) carbons would be positioned between the amine and the alkene; and to prepare an eight-membered ring, six (typically saturated) carbons would be positioned between the amine and the alkene. The resulting compound can be further functionalized as discussed above and exemplified in Scheme X below. See also Example 3 below for exemplary preferred reaction conditions.

Scheme X



In a preferred aspect, the invention provides new routes to substituted hydroxy ureas. More particularly, a protected hydroxy urea (e.g., a compound of the formula $NH_2C(O)NHOR$, where R is a hydroxy protecting group such as an alkyl, aryl or preferably aryalkyl ether such as an ether of an optionally substituted (phenyl)OCH_2-) is reacted with a substituted alcohol compound such as 21 of Scheme IV in the presence of suitable dehydrating agent(s) such as triphenyl phosphine and diethylazodicarboxylate (DEAD) to provide an amino ester, i.e. a moiety of the formula $-NRC(O)OR^1R$ where R is as defined immediately above and R^1 is a non-hydrogen group such as aryl, particularly phenyl, alkyl, e.g. C_{1-10} alkyl, etc. That amino ester is then treated with ammonia and a Lewis acid such as boron trifluoride etherate and the like to provide a hydroxy urea. In a preferred method of hydroxy urea formation, para-methoxybenzyl- is utilized as the hydroxy protection group R.

Compounds of the invention that have substituted nitrogen or sulfur alicyclic ring members (e.g. compounds of Formulae I through V wherein X is $-S(O)-$, $-S(O)_2-$, substituted N include -N(O)- can be readily prepared. For example, the prepared thio or nitrogen alicyclic group can be oxidized to provide a ring member of $-S(O)-$, $-S(O)_2-$, or -N(O)- by known techniques such as with H_2O_2 and/or sodium periodate. Where the nitrogen ring member is otherwise substituted, e.g. by an optionally substituted alkyl group, the preformed ring member can be reacted with an alkyl halide to provide the substituted nitrogen ring member.

As discussed above, compounds produced by the methods of the invention are useful for numerous therapeutic applications. The compounds can be administered to a subject, particularly a mammal such as human, in need of treatment, by a variety of routes. For example, the compound can be administered orally, parenterally, intravenously, intradermally, subcutaneously, or topically. For example, for parenteral application, particularly suitable are solutions, preferably oily or aqueous solutions as well as suspensions, emulsions, or implants, including suppositories. Ampules are

convenient unit dosages. For enteral application, particularly suitable are tablets, dragees or capsules e.g. having talc and/or carbohydrate carrier binder or the like, the carrier suitably being lactose and/or corn starch and/or potato starch.

It often will be preferable to use an optically active or enantiomerically enriched mixture of a chiral compound of the invention for a given therapeutic application. As used herein, the term "enantiometrically enriched" typically refers to a compound mixture that is at least approximately 70 mole%, 80 mole%, 85 mole% or 90 mole% of a single stereoisomer, and preferably a compound mixture that contains approximately at least about 92 mole%, 95 mole%, 97 mole%, 98 mole%, 99 mole% or 100% of a single enantiomer of the compound.

The active compound may be administered to a subject as a pharmaceutically active salt, e.g. salts formed by addition of an inorganic acid such as hydrochloric acid, hydrobromic acid, phosphoric acid, etc., or an organic acid such as acetic acid, oxalic acid, tartaric acid, succinic acid, etc. Base addition salts also can be formulated if an appropriate acidic group is present on the compound. For example, suitable base addition salts include those formed by addition of metal cations such as zinc, calcium, etc., or salts formed by addition of ammonium, tetraethylammonium, etc. Suitable dosages for a given therapy can be readily determined by the medical practitioner such as by standard dosing protocols. See also U.S. Patent 5,703,093.

All documents mentioned herein are incorporated herein by reference.

The following non-limiting examples are illustrative of the invention.

Example 1: Preparation of (2*S*)(5*R*,*S*)-2-(4-Fluorophenoxymethyl)-5-(4- N – hydroxy-ureidyl-1-butynyl)-tetrahydrothiophene (Scheme III, 11)

Part 1: (*R*)–Thiogylcidyl-4-fluorophenyl ether 2

Thiourea (6.5 g, 0.085 mol.) was added to a 250 ml two neck flask containing 140 ml of methanol and a magnetic stir bar. This solution was then cooled to 0 °C and (*R*)-glycidyl-4-fluorophenyl ether (13 g, 0.077 mol. in dry methanol) was added dropwise. The reaction mixture, while stirring, was allowed to warm to room temperature and stirred an additional 6 hours. During this time the reaction was monitored by TCL (ethyl acetate-light petroleum ether 1:4). Solvent was removed *in vacuo* and the residue was dissolved in ether, washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified on silica gel (9:1 hexane:ethyl acetate) to yield 10 g (70 %) of the ether 2, Scheme I. $[\alpha]_D = +13.3°$ (c 2.0, $CHCl_3$).

Part 2: (4*S*)-2-Carboethoxy-(4-fluorophenoxymethyl)-γ-thiobutyrolactone 3

Diethyl malonate (5.9 g, 0.0369 mol) and 40 ml of dry THF were added to a 100 ml two neck round bottom flask (equipped with a reflux condenser, nitrogen inlet and a septum). The reaction mixture was cooled to –78 °C and n-butyllithium was added dropwise and stirred for 45 minutes while allowed to warm. The mixture was then cooled to 0 °C and the fluorophenyl ether 2, 5.66 g, 0.031 mol., dissolved in THF was added. The reaction mixture was refluxed for 18 hours and monitored by TLC (ethyl acetate-light petroleum ether 1:3). The reaction was quenched with aqueous saturated ammonium chloride and solvent was removed. The resulting residue was dissolved in ethyl acetate, washed with brine then water, dried over Na_2SO_4 and concentrated to yield (4*S*)-2-Carboethoxy- (4-fluorophenoxymethyl)-γ-thiobutyrolactone 3 7.0 g. The crude product was purified on silica gel (ethyl acetate-light petroleum 1:8) to give 6.4 g (70 %) of 3,(Scheme I).

Part 3: (4*S*)-(4-Fluorophenoxymethyl)-γ-thiobutyroactone 4 (Scheme I) (4*S*)-2-Carboethoxy-(4-fluorophenoxymethyl)-γ-thiobutyrolactone 3, 6 g, 0.020 mol., was added to a 50 ml round bottom flask containing 30 ml of N,N-dimethylacetamide. $MgCl_2 \cdot 6\ H_20$ (4.08 g, 0.020 mol.) was added and the reaction mixture was refluxed for 6 hours. The reaction was diluted with water and extracted with ether. The organic layer was washed twice with water, brine and dried (Na_2SO_4). The solvent was removed in vacuo to afford the thiobutyrolactone 4 in 78 % yield, 3.5 g, m.p. 73 °C, $[\alpha]_D = +78$ ° (c 1.49, $CHCl_3$).

Part 4: (2*S*)(5*R*,*S*)-2-(4-Fluorophenoxymethyl)-5-hydroxy tetrahydrothiophene 5 (Scheme I)

(4*S*)-(4-Fluorophenoxymethyl)-γ-thiobutyrolactone 4, 2.57 g, 11.3 mol., in 25 ml of CH_2Cl_2 was added to a flame dried 50 ml two necked flask. The solution was cooled to –78 °C and DIBAL-H was added dropwise. The reaction was monitored by TLC (ethyl acetate:light petroleum 1:2). After 2 hours, the reaction was quenched with a saturated aqueous solution of sodium-potassium tartrate and extracted with CH_2Cl_2. The organic layer was washed twice with water, brine, dried (Na_2SO_4) and concentrated to afford the 5-hydroxy tetrahydrothiophene 5 in 96 % yield, 2.5 g.

Part 5: (2*S*)(5*R*,*S*)-5-Benzensulfonyl-2-(4-fluorophenoxymethyl)-5-(4-hydroxybutyn-1-yl)-tetrahydrothiophene 6 (Scheme II).

Benzenesulfinic acid (2.34 g, 16.4 mmol.) $CaCl_2$ (1.82 g, 16.4 mmol.) and 25 ml of CH_2Cl_2 were added to a 50 ml round bottom flask. The solution was cooled to 0 °C and (2*S*)(5*R*,*S*)-2-(4-Fluorophenoxymethyl)-5-hydroxy tetrahydrothiophene 5, 2.5 g, 0.011 mol., dissolved in dry CH_2Cl_2 was added. The reaction mixture was stirred and after 6 hours, filtered through celite and washed with CH_2Cl_2. The combined organic layers were washed with saturated aqueous Na_2CO_3, water, brine and dried over Na_2SO_4. Solvent was removed in vacuo and the resulting crude product was crystallized from chloroform-hexane to give the pure benzensulfonyl-tetrahydrothiophene 6 in 78 % yield, 3 g, m.p. = 84 °C.

Part 6: (2*S*)(5*R*,*S*)-2-(4-Fluorophenoxymethyl)-5-(4-tetrahydropyranoyl-1-butyne)-tetrahydrothiophene 7 (Scheme II).

Grignard grade magnesium, 0.81 g, 33.7 mmol, was added to a two necked round bottom flask and flamed dried under nitrogen. Dry THF, 70 ml, and 1,2-dibromoethane (cat.) were added sequentially to the activated magnesium. Next, isopropyl bromide (2.07 g, 16.8 mol.) dissolved in THF was added dropwise over 10 minutes and the reaction was stirred for 1 hour. The resulting isopropyl magnesium bromide was cannulated into a 100 ml flame dried round bottom flask. 4-Tetrahydropyranoyl-1-butyne, 2.60 g, 16.8 mmol., was added and the reaction mixture was stirred at room temperature for 30 minutes and then cooled to 0 °C. $ZnBr_2$, (10.12 ml, 1 M in THF) was added to the cooled mixture and stirred for 45 minutes. The reaction mixture was allowed to warm to room temperature and (2*S*)(5*R*,*S*)-5-Benzensulfonyl-2-(4-fluorophenoxymethyl)-5-(4-hydroxybutyn-1-yl)-tetrahydrothiophene 6 (2.97 g, 8.4 mmol.) in THF was added. The reaction mixture was refluxed till completion of reaction with monitoring by TCL (ethyl acetate:light petroleum 1:4). At the end of 16 hours, the reaction was cooled to 0 °C and quenched with saturated aqueous NH_4Cl. THF was removed in vacuo and the reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated to yield 3 g of the crude tetrahydropyranoyl derivative 7.

Part 7: (2*S*)(5*R*,*S*)-2-(4-Fluorophenoxymethyl)-5-(4-hydroxybutyn-1-yl)-tetrahydrothiophene 8, (Scheme II)

Crude (2*S*)(5*R*,*S*)-2-(4-fluorophenoxymethyl)-5-(4-tetrahydropyranoyl-1-butyne)-tetrahydrothiophene 7 (3 g) was dissolved in 5 ml of methanol. A solution of 1 % HCl in methanol (10 ml) was added and the reaction was stirred at room temperature with monitoring by TLC (ethyl acetate:light petroleum ether 1:1). At the end of 4 hours the reaction mixture was neutralized with saturated aqueous Na_2CO_3 and methanol was removed in vacuo. The resulting solution was extracted with ethyl acetate, washed with

water, brine, dried (Na_2SO_4) and concentrated. The reaction residue was dried in vacuo with warming to give *(2S)(5R,S)*-2-(4-Fluorophenoxymethyl)-5-(4-hydroxybutyn-1-yl)-tetrahydrothiophene 8 in 86 % yield, 2.05 g.

Part 9: (2*S*)(5*R*,*S*)-2-(4-Fluorophenoxymethyl)-5-(4-N,O-biscarbophenoxy-1-butynyl)-tetrahydrothiophene 10 (Scheme III)

A solution of dry THF (20 ml) and (2*S*)(5*R*,*S*)-2-(4-fluorophenoxymethyl)-5-(4-hydroxybutyn-1-yl)-tetrahydrothiophene 9, 1.86 g 6.6 mol., was cooled to 0 °C. Diethylazodicarboxylate, 1.4 g, 8.0 mol., was added dropwise followed by triphenylphosphine, 2.09 g, 8.0 mmol., and the reaction mixture was stirred at 0 °C. N,O-biscarbophenoxy hydroxylamine, 2.18 g, 8.0 mmol, was added to the cooled reaction mixture and stirred for 6 hours with warming to room temperature. The reaction was monitored by TLC (hexane:ethyl acetate 3:1). Upon completion, solvent was removed in vacuo and the resulting crude residue was dissolved in ethyl acetate which was subsequently washed with water, brine, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel (hexane:ethyl acetate 6:1) to give 3.4 g (96 %) of (2*S*)(5*R*,*S*)-2-(4-Fluorophenoxymethyl)-5-(4- N,O-biscarbophenoxy-1-butynyl)-tetrahydrothiophene 10.

Part 10: *(2S)(5R,S)*-2-(4-Fluorophenoxymethyl)-5-(4-N–hydroxy-ureidyl-1-butynyl)-tetrahydrothiophene 11 (Scheme III)

A solution of methanol (5 ml) and *(2S)(5R,S)*-2-(4-fluorophenoxymethyl)-5-(4-N,O-biscarbophenoxy-1-butynyl)-tetrahydrothiophene 10 (3.0 g, 5.6 mmol.) was added to a 50 ml round bottom flask. Saturated NH_3-MeOH, 15 ml, was added to the reaction mixture and allowed to stir for 12 hours. Solvent was removed in vacuo and the resulting crude residue was crystallized from ethyl acetate-hexane to get pure *(2S)(5R,S)*-2-(4-Fluorophenoxymethyl)-5-(4- N –hydroxy-ureidyl-1-butynyl)-tetrahydrothiophene 11 in 63 % yield, 1.2g, m.p. = 117 °C.

Example 2: Preparation of (2S,5S)-2-(4-fluoro)phenoxymethyl-5-(4-hydroxyureidyl-1-butynyl)pyrrolidine

References in this Example 2 to compound numerals (generally underlined) designate the compounds depicted structurally in Scheme IX above.

Part 1: (S)-5-Methoxycarbonyl-1-(4-methoxybenzyl)-2-pyrrolidinone (Scheme IX; 1) :

To a solution of (S)-glutamic acid (50g, 0.34 mmol) in 300 ml. of 2M NaOH, was added a solution of p-anisaldehyde (46.3g, 0.34 mmol) in ethanol (50ml). Following stirring for 30 min., the reaction mixture was cooled to 0^0C and sodium borohydride (3.8g, 0.1 mmol) was added in portions. After being stirred for 2h at room temperature, an additional amount of p-anisaldehyde (4.6g, 0.033 mmol) was added , followed by stirring for 30 min. and then addition of $NaBH_4$ (0.25 g , 0.006 mmol). After stirring for 30 min., the reaction mixture was extracted with ether (3x300 ml). The pH of the aqueous layer was adjusted to approximately 3 by dropwise addition of conc. HCl at 0^0C. The precipitated solid was filtered off, dried and then dissolved in 700 ml of ethanol. After refluxing for 5 hours, the solution was concentrated and the residue taken in methylene chloride to filter off the undissolved material. The clear solution on solvent removal gave 20 g of crude product (24%).

To that crude product dissolved in 500 ml of dry methanol, under N_2 atm., thionyl chloride (2ml) was added slowly for 2 min. After being stirred for 12 hours at room temperature, aqueous saturated $NaHCO_3$ was added dropwise until neutral pH. The solvent was dried under vacuo and the residue was dissolved in ethyl acetate , washed with water and brine , dried over anhydrous Na_2SO_4 and concentrated to afford the crude product which on purification by column chromatography (20% ethyl acetate in hexane, 60-120 mesh) gave 20 g of pure product as colorless oil (95%)

^{1}H NMR (200 MHz, $CHCl_3$): δ 1.9 - 2.63 (m, 4 H), 3.65 (s, 3H), 3.77 (s, 3H), 3.83-4.00 (m, 2H), 4.82- 4.98 (d, 2H, J=13.6 Hz), 6.73-6.85 (d, 2H, J = 7.9 Hz), 7.02-7.16 (d, 2H, J= 7.9 Hz).

Part 2: (S)-5-hydroxymethyl-1-(4-methoxybenzyl)-2-pyrrolidinone (Scheme IX; 2):

Lithium chloride (8.17g, 190mmol) and sodium borohydride (7.2g, 190 mmol) were taken in a solvent mixture of ethanol (100 ml) and THF (60 ml) at 0^0C. After vigorous stirring for 1 hour at room temperature, a solution of (S)-5-Methoxycarbonyl-1-(4-methoxybenzyl)-2-pyrrolidinone (20g, 76 mmol) (prepared as in Part 1 above) in 40 ml of THF was added at 0^0C. The reaction mixture was stirred at room temperature for 6 hours. The solid was filtered off. The filtrate was neutralised to pH approximately 7 by dropwise addition of saturated aqueous NH_4Cl solution at O^0C. The solvent was removed under vaccuo. The residue was partitioned between ethyl acetate (500 ml) and water (500 ml). The organic extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vaccuo to afford the crude product as colorless solid (17g, 95%) which was almost pure to be telescoped. ^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.9 - 2.1 (m, 2H), 2.2-2.55 (m, 3H), 2.55-2.65 (1H, br s,-OH), 3.35-3.52 (m, 2H), 3.7-3.85 (d, 4H), 4.02-4.15 (d, 1H, J=13.6 Hz), 4.70-4.85 (d, 1H, J=13.6 Hz), 6.73-6.85 (d, 2H, J= 7.9 Hz), 7.10-7.20 (d , 2H, J=7.9 Hz). TLC specification: mobile phase = 75% ethyl acetate in hexane; stat. phase = fsg 254; visual method = anisal stain, apm stain and uv; and Rf values = starting material : 0.2 and pdt. : 0.5.

Part 3: (S)-1-(4-methoxybenzyl)-5-p-tolunesulphonyloxymethyl-2-pyrrolidinone (Scheme IX; 3):

A mixture of (S)-5-hydroxymethyl-1-(4-methoxybenzyl)-2-pyrrolidinone (5g, 21.28 mmol), p-tolunesulphonyl chloride (4.46g, 23.5mmol), triethylamine (4.3g, 42.56 mmol) in 75 ml of methylene chloride was stirred for 12 hours at room temperature. After washing with saturated aqueous $NaHCO_3$ and water, the organic layer was dried over

anhydrous Na_2SO_4 and concentrated to afford the crude product which was filtered through a silica gel column (50% ethyl acetate in hexane, 60-120 mesh) to afford pure product as colorless solid in quantitative yield (7.5g, 90%). ^{1}H NMR (200MHz, $CDCl_3$) :δ 1.73-1.93 (m, 1H), 1.96-2.18 (m, 1H), 2.24-2.60 (m, 5H), 3.63 (sex, 1H, J=3.5Hz), 3.74 (d, 2H, J= 14 Hz), 3.8 (s, 3H), 3.90-4.10 (m, 2H), 4.85 (d, 2H, J=14 Hz), 6.82 (d, 2H, J=8.13 Hz), 7.08 (d, 2H, J= 8.13 Hz), 7.38 (d, 2H, J=8.13 Hz), 7.75 (d, 2H, 8.13Hz) TLC specification : mobile phase = pure ethyl acetate; stat. phase = fsg 254; visual method= anisaldehyde stain, apm stain and uv; Rf values = starting material : 0.2 and pdt. : 0.6.

Part 4: (S)-1-(4-methoxybenzyl)-5-(4-fluoro)phenoxymethyl-2-pyrrolidinone (Scheme IX; 4):

To a solution of 4-fluorophenol (8.6g, 77mmol), in 50 ml of dry DMF, sodium hydride (3.08g, 77mmol) was added spanning for 5 min. at 0^0C under N_2 atmosphere. Stirring for 15 min at room temperature was followed by the addition of a solution of (S)-1-(4-methoxybenzyl)-5-p-tolunesulphonyloxymethyl-2-pyrrolidinone (20g, 51.3mmol) in 100 ml of dry DMF and TBAI (0.33g, 9mmol). The reaction was stirred for 3 hours. Ice-cold water (500 ml) was then added followed by extraction with ethyl ether (3x500ml). The combined organic extract was washed with water and brine, dried over anhydrous Na_2SO_4 to afford a brown syrup which was purified by column chromatography (50% ethyl acetate in hexane, 60-120 mesh) to afford the colorless solid (16g, 89%) as pure product. ^{1}H NMR (200MHz, $CDCl_3$): δ 1.8-2.0 (m, 1H), 2.0-2.22 (m, 1H), 2.24-2.64 (m, 2H), 3.67 (s, 3H), 3.72-3.83 (m, 3H), 4.02 (d, 2H, J=15.90 Hz), 4.78 (d, 2H, J=15.90Hz), 6.54-6.64 (m, 4H), 6.84 (d, 2H, J=8.0 Hz), 7.07 (d, 2H, J=8.0Hz). ^{13}C NMR (50MHz, $CDCl_3$): δ 21.68, 30.16, 44.27, 55.14, 56.39, 69.15, 113.96, 115.34, 115.54, 116.0, 128.81, 129.24, 175.25. IR ($CHCl_3$, cm^{-1}) : 2904, 1688, 1504, 1440, 1248, 1040, 840 FABMS (m/z) :121, 204, 222, 330(M^++1). HRMS : calcd. 330.150547, found 330.152029 , Melting point : 62-63^{0}C. $[\alpha]_D$: 5.51 (C 6.02, $CHCl_3$). TLC specification: mobile phase = 50% ethyl acetate in hexane (quadraple runs); stat. phase = fsg 254;

visual method = anisaldehyde stain, apm stain and uv; Rf values = starting material : 0.2 and pdt. : 0.6.

Part 5: (S)-5-(4-fluoro)phenoxymethyl-2-pyrrolidinone (Scheme IX; 5) :

(S)-1-(4-methoxybenzyl)-5-(4-fluoro)phenoxymethyl-2-pyrrolidinone (11g, 54.4mmol), and ceric ammonium nitrate (89.5g, 163.2mmol) were taken in a mixture of acetonitrile (160 ml) and water (16ml). The reaction mixture was stirred for 2 hours. The solvent was removed under vacuo. Ethyl acetate (300ml) was added and the insoluble inorganic material was filtered off. The filtrate was washed with water, and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuo to leave a brown residue which on purification by column chromatography (pure ethyl acetate, 60-120 mesh) afforded 8.74 g of pure product (77%). ^{1}H NMR (200MHz, $CDCl_3$) : δ 1.8-2.08 (m, 1H), 2.24-2.5 (m, 3H), 3.7-3.87(d, 1H, J=8.13Hz), 3.88-4.00 (dd, 1H, J_1=9.3 Hz, J_2=3.50Hz), 4.0-4.15 (m, 1H), 6.23-6.40 (br s, 1H), 6.72-6.90 (dd, 2H, J_1=9.3Hz, J_2=3.50Hz), 6.91-7.05 (t, 2H, 8.4Hz). ^{13}C NMR (50MHz, $CDCl_3$): δ 23.13, 29.60, 53.33, 71.90, 115.51, 115.63, 116.10, 178.10. IR (neat, cm^{-1}) : 820, 1204, 1352, 1648, 2876, 3212. EIMS (m/z) : 210(M^++1), 117, 101, 84, 73, 60. HRMS : calcd. 210.093032 , found 209.085099 Melting point : 90-91^{0}C. $[\alpha]_D$: 59.36 (C 0.85, $CHCl_3$). TLC specification: mobile phase = pure ethyl acetate; stat. phase = fsg 254; visual method = anisaldehyde, apm stain and uv; Rf values = starting material : 0.8 and pdt. : 0.3.

Part 6: (5S)-1-*tert*-butyloxycarbonyl-2-(4-fluoro)phenoxymethyl pyrrolidinone (Scheme IX; 6) :

(S)-5-(4-fluoro)phenoxymethyl-2-pyrrolidinone (8.24 g, 39.8 mmol) and DMAP (4.86g, 39.8 mmol) were taken in 100 ml of dry THF under N_2 atmosphere . Di-*tert*-butyl dicarbonate (17.4g, 79.6 mmol) was then added dropwise at RT. After a period of 5h stirring, the solvent was removed under vacuo. The residue was triturated with a mixture of ethyl acetate and petroleum ether (1 : 3 ratio, 200 ml) and the precipitated material was filtered off. The filtrate was washed with brine, dried over anhydrous

Na_2SO_4, and concentrated to afford the residue which was purified by column chromatography (5% ethyl acetate in hexane, 60-120 mesh) providing the pure product as a colourless oil (10.5g, 86%). ^1H NMR (200MHz, $CDCl_3$) : δ 1.54 (s, 9H), 2.13-2.36 (m, 2H), 2.38-2.58 (dddd, 1H, J_1= 2.04Hz, J_2= 10.2 Hz, J_3 = 13.3 Hz), 2.69-2.91 (m, 1H), 4.02-4.22 (m, 2H), 4.4-4.52 (m, 1H), 6.82 (dd, 2H, J_1= 4.08 Hz, J_2= 10.2 Hz), 6.97 (t, 2H, J= 8.16Hz). ^{13}C NMR (50MHz, $CDCl_3$) : δ 21.13, 28.05, 31.87, 56.63, 69.15, 96.11, 115.49, 115.65, 116.12, 160.00, 174.00. IR (neat, cm^{-1}) : 2992, 1792, 1712, 1504, 1472, 1376, 1312, 1264, 1200, 1152, 1024, 832. EIMS (m/z) :107,142, 152, 179, 210, 232, 254, 310(M^++1). HRMS : calcd. 309.137637, found 309.136584. Melting point : 75 - 76^{0}C. $[\alpha]_D$: - 71.36 (C 3.08, $CHCl_3$). TLC specification: mobile phase = pure ethyl acetate; stat. phase = fsg 254; visual method = anisaldehyde, apm stain and uv; Rf values = starting material : 0.3 and pdt.: 0.9.

Part 7: (5S)-1-*tert*-butyloxycarbonyl-5-(4-fluoro)phenoxymethylpyrrolidin-2-ol (Scheme IX; 7) :

To a cooled solution of (5S)-1-*tert*-butyloxycarbonyl-5-(4-fluoro)phenoxymethyl pyrrolidinone (10g, 32.3mmol) at -78^{0}C under N_2 atmosphere in dry DCM (100ml) was added DIBAL-H (1M solution in toluene, 34 ml, 32.3mmol) dropwise. The reaction mixture was stirred for 1hour. Saturated aqueous Rochelle's salt solution (20ml) was added and the reaction mixture was stirred for 1h. The precipitated solid was filtered off. The filtrate was dried over anhydrous Na_2SO_4 and concentrated to afford 10g of crude product as colorless oil (100%). ^1H NMR (200MHz, $CDCl_3$): δ 1.52 (s, 9H), 1.80-2.42 (m, 4H), 3.6-4.25 (m, 3H), 5.32-5.6 (m, 1H), 6.77-7.3 (m, 4H). TLC specification: mobile phase = 20% ethyl acetate in hexane; stat. phase = fsg 254; visual method = anisaldehyde, apm stain and uv; Rf values = starting material : 0.4 and pdt. : 0.8

Part 8: (5S)-1-*tert*-butyloxy-5-(4-fluoro)phenoxymethyl -2-methoxypyrrolidine (Scheme IX; 8) :

(5S)-1-*tert*-butyloxycarbonyl-5-(4-fluoro)phenoxymethylpyrrolidin-2-ol(10g,32.15mmol) and PPTS (0.8g, 3.2mmol) were taken in 100 ml of methanol. After being stirred for 18h at RT, evaporation of the solvent gave the residue which on purification by column chromatography afforded 10g of pure product as colorless oil (96%). ^{1}H NMR (200MHz, $CDCl_3$) : δ 1.5 (s, 9H), 1.75-2.25 (m, 4H), 3.23-3.5 (m, 3H), 3.72-3.9 (m, 1H), 4.02-4.38 (m, 2H), 5.1-5.5 (m, 1H), 6.76-7.02 (m, 4H). IR (neat, cm^{-1}): 2976,2944, 1696,1504,1392,1208, 1186, 1078,824. TLC specification: mobile phase = 20% ethyl acetate in hexane; stat. phase = fsg 254; visual method = apm stain and uv; Rf values = starting material : 0.3 and pdt. : 0.5.

Part 9: (5S)-2-benzenesufonyl-1-*tert*-butyloxy -5-(4-fluoro)phenoxy methylpyrroilidine (Scheme IX; 9):

A solution of (5S)-1-*tert*-butoxy-5-(4-fluoro)phenoxymethyl-2-methoxy pyrrolidine (9.8g, 30.15mmol) in dry DCM (100ml) containing powdered $CaCl_2$ (5g) was cooled to 0^0C. Freshly prepared benzenesulfinic acid (4.3g, 30.15 mmol) was then added at once. The reaction mixture was, after being stirred for 2h at ambient temperature, was cooled back to 0^0C. Aqueous saturated $NaHCO_3$ solution was added and the stirring was continued for 1h. The suspension was filtered off and the filtrate was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated to afford 11.8g of pure product as colorless solid. (90%). ^{1}H NMR (200MHz, $CDCl_3$) : δ 1.20 (s, 9H), 2.1-2.57 (m, 3H), 2.7-2.83 (m, 1H), 4.07-4.52 (m, 3H), 5.1-5.25 (m, 1H), 6.87-7.07 (m, 4H), 7.48-7.77 (m, 3H), 7.85-7.97 (m, 2H). IR (neat, cm^{-1}): 2976,1752,1504, 1488, 1456, 1368, 1312, 1216, 1152, 1088, 1040, 832, 768, 688, 560. FABMS (m/z) : 125,154, 194, 195, 194, 434, 435, 436 (M^++1). HRMS: calcd. 436.159398, found 436. 162468. Melting point: 113-114^{0}C TLC specification: mobile phase = 20% ethyl acetate in hexane; stat. phase = fsg 254; visual method = apm stain and uv; Rf values = starting material : 0.55 and pdt. : 0.3;

Part 10: (2S,5S)-1-*tert*-butoxycarbonyl-2-(4-fluoro)phenoxymethyl-5-(2-hydroxyethyl)ethynyl pyrrolidine (Scheme IX; 10) :

To a solution of 1-tetrahydropyranyloxy-3-butynylmagnesium bromide in THF (prepared in situ by the addition of isopropylmagnesium bromide in THF) to 2-(3-butynyl-1-oxy)tetrahydropyran (1.078g, 7mmol)), was added a solution of zinc bromide in THF (0.78g, 3.5mmol) at ambient temperature. To the colorless suspension, formed after 30 min. of stirring, was added (5S)-2-benzenesufonyl-1-*tert*-butoxycarbony-5-(4-fluoro)phenoxymethylpyrrolidine (1.5g, 3.5mmol) in 12 ml of THF. The reaction mixture was stirred for 10 hours. The reaction mixture was quenched with aqueous NH_4Cl solution (3ml) and partitioned between ether (300ml) and water (100ml). The organic part was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to afford the crude product which was dissolved in methanol (15ml). PPTS (66mg, 0.26mmol) was added and the reaction mixture was stirred at room temperature overnight. The residue after the removal of methanol, was purified by column chromatography (60-120mesh, 30% ethyl acetate in hexane) to afford the pure product as colorless oil (1.0g, 86%). ^1H NMR(200 MHz,$CDCl_3$) : δ 1.49 (s,9H), 1.55-1.82(m,2H), 1.87-2.0(m,1H), 2.0-2.3(m,2H), 2.35-2.5(m,2H), 3.6-3.75(t,2H), 3.75-3.9(m,1H), 3.95-4.25(m,2H), 4.44-4.58(m,1H), 6.77-7.0(m,4H). FABMS(m/z): 107, 136, 138, 154, 194, 238, 264, 308, 364.(M^++1). TLC specification: mobile phase = 30% ethyl acetate in hexane; stat. phase = fsg 254; visual method = apm stain and uv; Rf values = starting material : 0.85 and pdt.: 0.4.

Part 11: (2S,5S)-1-*tert*-butoxycarbonyl-2-(4-fluoro)phenoxymethyl-5-(4-N,O-bis-phenoxycarbonylhydroxyamino-1-butynyl)pyrrolidine (Scheme IX; 11):

To a solution of (2S,5S)-1-*tert*-butoxycarbonyl-5-(2-hydroxyethyl)ethynyl-2-(4-fluoro)phenoxymethylpyrrolidine (820mg, 2.26mmol), triphenyphosphine (712mg, 2.7mmol) and N,O-bis-phenoxycarbonylhydroxylamine (0.7g, 2.7mmol) was added diethyl azodicarboxylate (0.47 g, 2.7mmol) dropwise. After being stirred for 30 min. at 0^0C, the stirring was continued for 6h at RT. The solvent removal under vacuo and the

subjection of the residue to column purification (30% ethyl acetate in hexane,60-120 mesh) to afford colorless semi-solid (1.12,80%). ^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.5 (s, 9H), 1.88-2.4 (m, 4H), 2.62-2.77 (t, 2H), 3.65-4.29 (m, 5H), 4.4-4.6 (m, 1H), 6.76-7.1 (m, 4H), 7.1-7.3 (m, 6H), 7.3-7.5 (m, 4H). TLC specification: mobile phase = 30% ethyl acetate in hexane; stat. phase = fsg 254; visual method = apm stain and uv; Rf values = starting material : 0.3and pdt. : 0.7.

Part 12: (2S,5S)-1-*tert*-butoxycarbonyl-5-(2-hydroxyethyl)ethynyl-2-(4-fluoro)phenoxymethyl-5-(4-hydroxyureidyl-1-butynyl)pyrrolidine (Scheme IX; 12) :

Ammonia gas was purged into a solution of (2S,5S)-1-*tert*-butoxycarbonyl-5-(2-hydroxyethyl)ethynyl-2-(4-fluoro)phenoxymethyl-5-(4-N,O-bis-phenoxycarbonylhydroxy amino-1-butynyl)pyrrolidine (1.4g, 2.26mmol) in a solvent mixture of methanol (30ml) and THF (10 ml) at 0^0C for 15 minutes. The reaction mixture was stirred for 6 hours at room temperature overnight. Evaporation of the solvent and purification of the residue by column chromatography (30% ethyl acetate in hexane, 60-120 mesh) to afford 0.81 g of pure product as colorless liquid (85%). ^{1}H NMR (200MHz, $CDCl_3$): δ 1.5 (s, 9H), 1.85-2.31 (m, 4H), 2.36-2.5 (t, 2H), 3.5-3.68 (m, 1H), 3.69-3.90 (m, 2H), 3.93-4.4 (dd, 1H, J= 7.9 Hz, J=3.4Hz), 4.07-4.2 (m, 1H), 4.35-4.55 (m, 1H), 5.1-5.35 (br.s, 2H), 6.73-7.0 (m, 4H). IR (neat, cm^{-1}) : 3504, 3450-3000 (br.), 2960, 1688, 1512, 1392, 1208,1160, 760. FABMS(m/z) : 153,194, 274, 322, 388, 422 (M^++1). TLC specification: mobile phase = 30% ethyl acetate in hexane; stat. phase = fsg 254; visual method = apm stain and uv; Rf values = starting material : 0.9 and pdt.: 0.6.

Part 13: (2S,5S)-2-(4-fluoro)phenoxymethyl-5-(4-hydroxyureidyl-1-butynyl)pyrrolidine (Scheme IX; 13):

Trifluoroacetic acid (0.5ml, 5.49mmol) was added to a solution of substrate (0.8g, 1.83mmol) in 10ml of DCM at 0^0C. The reaction mixture was stirred for 3 hours at room temperature. Aqueous saturated $NaHCO_3$ was added at 0^0C. After being stirred for 10

min. the organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 and concentrated to afford the brown residue which was purified by column chromatography (10%methanol in ethyl acetate) to afford the colorless semi-solid (0.55g, 86%). ^{1}H NMR(200 MHz,$CDCl_3$) : δ 1.5-1.97 (m, 4H), 2.01-2.25 (m, 2H), 2.38-2.6 (t, J=2.17Hz, 2H), 3.52-3.7 (t, J=6.54Hz, 2H), 3.72-4.04 (m, 4H), 6.73-7.6 (m, 4H). FABMS(m/z) : 107, 120, 124, 136, 138, 154, 176, 194, 268, 279, 322 (M^++1). TLC specification: mobile phase = 5% methanol in ethyl acetate; stat. phase = fsg 254; visual method = apm stain and uv; Rf values = starting material : 0.2 and pdt. : 0.6

Example 3 Further preparation of (2S,5S)-2-(4-fluoro)phenoxymethyl-5-(4-hydroxyureidyl-1-butynyl)pyrrolidine

References in this Example 3 to compound numerals (generally underlined) designate the compounds depicted structurally in Scheme X above.

Part 1: (R)-1-(4-fluorophenyl) glycerol (Scheme X: 1):

To a solution of 4-fluorophenol (40g, 0.35mmol) in 400ml acetone were added K_2CO_3 (148g,1.05mmol) and epichlorohydrin (98g, 1.05mmol). The reaction mixture was refluxed for 12 hr. Acetone was removed under vacuum, the residue was yl acetate, washed with water, dried over Na_2SO_4 and concentrated . The crude residue was distilled at 120°C, 2.0mm vacuum to get glycidyl-4-fluorophenyl ether product (52g, 85% yield). To the racemic glycidyl-4-fluorophenyl ether (52g, 0.31mmol) was added (R, R) Co-Salen complex (1.03g, 1.54mmol). Distilled water (3.06ml, 0.17mmol) was added dropwise to the reaction over a period of 1h. The reaction was stirred for 12hr and completion of the reaction was judged by HPLC. Hexane was added in the reaction mixture and the compound which got precipitated out was filtered and further washed with hexane to afford pure white solid (R)-1-(4-fluorophenyl)glycerol (26.38g,49% yield);TLC ethylacetate-hexane (1:3) R_f=0.2; $[\alpha]_D$-9.6° (c 1.6, EtOH) ;97% ee.

Part 2: (R)-Glycidyl-4-fluorophenyl ether (Scheme X; 2):

A mixture of (R)-1-(4-fluorophenyl)glycerol (26g, 0.14mmol), triphenylphosphine (52g, 0.21mmol) in dry benzene (250ml) were taken in a 500ml R.B. flask equipped with a spinbar, reflux condenser and nitrogen inlet. Diethylazodicarboxylate (DEAD) (33.3g, 0.21mmol) was added to it and the reaction mixture was heated under reflux for 18h. Solvent was removed on rotavapor and the residue was dissolved in ether, washed with water, brine, dried over Na_2SO_4, concentrated and purified by silica gel column chromatography to give pure title product 2 (12.5g, 54.3% yield): TLC: ethyl acetate-hexane (1:4), R_f=0.5; $[\alpha]_D$-4.9° (c1.46, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 200MHz): δ 2.68 (dd, J = 4.5, 2.2 Hz, 1H), 2.85 (t, J = 4.58Hz,1H), 3.27 (m, 1H), 3.89 (dd, J = 15.7, 6.7Hz, 1H), 4.11 (dd, J = 15.7, 4.5Hz, 1H), 6.74 -7.02 (m, 4H).

Part 3: (2R)-1-(4-fluorophenyl) hex-5-ene,2-ol (Scheme X; 3) :

A 500ml two neck flask equipped with a magnetic stir bar, reflux condenser a septum and a nitrogen inlet, was charged with magnesium (8.5g, 0.35mmol) and flame dried along with magnesium. Dry ether (30ml) and dibromoethane (1ml) were introduced. The reaction mixture was maintained at 0°C and ice water circulation was maintained through the condenser. Allyl bromide (9.1ml, 0.11mmol) in dry ether (50ml) was added dropwise. The reaction mixture was stirred for 1h and then CuCN (130mg) was added. 4-fluorophenyl-glycidyl ether 2 (12g, 0.07mmol) in 120ml of dry ether was introduced slowly after 10 min. The reaction was completed in 20 min. as judged by TLC in 30% ethylacetate-hexane (R_f= 0.6). Saturated ammonium chloride was added to quench the reaction and then the mixture was partitioned between water-ethylacetate. Ethylacetate layer was washed with brine, dried over Na_2SO_4 and concentrated to give title product 3 (13.5g, 90 %), $[\alpha]_D$ -20.6 (c1.0,$CHCl_3$). ^{1}H-NMR ($CDCl_3$, 200MHz): δ 1.62-1.73 (m. 2H), 2.18-2.43 (q, J=6.8Hz, 2H), 3.75-4.09 (m, 3H), 4.96-5.17 (m, 2H), 5.73-5.96 (m, 1H), 6.78-7.02 (m, 4H).

Part 4: (2S)-1-(4-flourophenyl)-2-phthalimido-hex-5-ene (Scheme X; 4) :

To a solution of compound 3 (8.4g, 0.04mmol) in dry THF maintained at 0°C and under nitrogen, was added phthalimide (7.0g, 0.048mmol) and triphenylphosphine (12.6g, 0.48mmol) . After 10min DEAD (7.6ml, 0.048mmol) was added dropwise. The reaction was stirred for 5h and the completion was judged by TLC, 20% ethyl acetate - hexane ($R_f = 0.7$). THF was removed in vacuum and the residue was partitioned between water-ethyl acetate. The ethyl acetate layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified on silica gel using ethyl acetate-hexane to give title product 4. ^{1}H-NMR ($CDCl_3$, 200MHz) : δ 1.86-2.39 (m, 4H), 4.12-4.21 (dd J=4.5Hz, 13.6Hz , 1H), 4.43-4.55 (t, J=9Hz, 1H), 4.57-4.75(m, 1H), 4.89-5.14(m,2H), 5.65-5.87 (m, 1H), 6.69-7.05 (m, 4H), 7.63-798 (m, 4H). Mass : 340 (M^++1).

Part 5: (2S)-1-(4-flourophenyl)hex-5-ene-2-amine (Scheme X; 5)

To a boiling solution of compound 4 (7.2g , 0.02mmol) in 100 ml of ethanol was added hydrazine hydrate (1.5ml , 0.03mmol). The reaction mixture was refluxed for 4h and cooled to 0°C. Ethanol was removed under vacuum and partitioned between water-ethyl acetate. The ethyl acetate layer was separated, dried over Na_2SO_4 , concentrated to get free amine 5 (4g) which was used as such for the next reaction. ^{1}H-NMR ($CDCl_3$, 200MHz) : δ 1.54-1.8 (m, 2H), 2.12-2.38 (m, 2H), 3.09-3.3 (broad s, 2H), 3.64-3.78 (m, 1H), 3.8-3.98 (m, 2H), 4.95-5.18 (m, 2H), 5.72-5.96 (m, 1H), 6.75-7.1 (m, 4H).

Part 6: (2S)-1-(4-fluorophenyl)hex-5-ene-2-N-tributyloxycarbonyl amine (Scheme X; 6)

To a solution of compound 5 (3.8g, 0.01mmol) in 40ml THF was added triethyl amine (1.2ml, 0.01mmol) and $(Boc)_2O$ (2.1ml, 0.013mmol). The reaction mixture was stirred for 4h and the completion of the reaction was judged by TLC (15% ethyl acetate-hexane, $R_f = 0.8$) . The residue was concentrated, diluted with ethyl acetate, washed with water and brine, dried over Na_2SO_4 and concentrated under vacuum to give title product 6 (4.6g), which was purified on silicagel column. The overall yield of the two step i.e. from

compound 4-6 is 70 %. ^{1}H-NMR ($CDCl_3$, 200MHz): δ 1.38-1.43 (s, 9H), 1.67-1.82 (m , 2H), 2.19-2.23 (q, J=4.5Hz, 2H), 3.82-3.98 (s, 3H), 4.6-4.76 (broad s, 1H), 4.92-5.1 (m,2H), 5.7-5.9 (m, 1H), 6.74-7.03 (m, 4H). Mass : 310 (M^++1)

Part 7: (5S)-1-*tert*-butyloxycarbonyl-5-(4-fluoro)phenoxymethylpyrrolidin-2-ol (Scheme X; 7) :

To a solution of compound 6 (3g) in dry methylene chloride (50ml) was subjected to ozonolysis and stirred for 2 hours at -78°C. The completion of the reaction was judged by TLC in 20% ethylacetate-hexane (R_f = 0.8). The reaction was quenched with dimethylsulphate, and concentrated to afford 10g of crude product (1.5g). ^{1}H NMR (200MHz, $CDCl_3$): δ 1.52 (s, 9H), 1.80-2.42 (m, 4H), 3.6-4.25 (m, 3H), 5.32-5.6 (m, 1H), 6.77-7.3 (m, 4H). HRMS: cal :311.1532, found: 311.1545

Part 8: (5S)- 1-*tert*-butoxycarbonyl -5-(4-fluoro)phenoxymethyl -2-methoxypyrrolidine (Scheme X; 8) :

(5S)-1-*tert*-butyloxycarbonyl-2-(4-fluoro)phenoxymethylpyrrolidin-2-ol (1.0g, 0.32mmol) and PPTS (8mg, 0.32mmol) were taken in 10ml of methanol. After being stirred for 18h at room temperature, evaporation of the solvent gave a residue which on purification on silicagel column afforded 1.0g (96%) of pure product, TLC : 20% ethylacetate-hexane R_f= 0.5. ^{1}H NMR (200MHz, $CDCl_3$): δ 1.5 (s, 9H), 1.75-2.25 (m, 4H), 3.23-3.5 (m, 3H), 3.72-3.9 (m, 1H), 4.02-4.38 (m, 2H), 5.1-5.5 (m, 1H), 6.76-7.02 (m, 4H).

Part 9: (5S)-2-benzenesufonyl-1-*tert*-butoxycarbony-5-(4-fluoro)phenoxymethyl pyrrolidine (Scheme X; 9) :

A solution of (5S)-5-(4-fluoro)phenoxymethyl-1-*tert*-butoxycarbonyl-2-methoxypyrrolidine (0.9g, 3.015mmol) in dry DCM (10ml) containing powdered $CaCl_2$ (0.5g) was cooled to 0^0C. Freshly prepared benzenesulfinic acid (0.43g, 3.015 mmol) was then added at once. The reaction mixture was stirred for 2h at ambient temperature

and then cooled back to 0^0C. Aqueous saturated $NaHCO_3$ solution was added and the stirring was continued for 1hour. The suspension was filtered and the filtrate was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated to afford 1.18g of pure product (90%), TLC was done in 20% ethylacetate-hexane, $R_f = 0.4$.
^1H NMR (200MHz, $CDCl_3$) : δ 1.20 (s, 9H), 2.1-2.57 (m, 3H), 2.7-2.83 (m, 1H), 4.07-4.52 (m, 3H), 5.1-5.25 (m, 1H), 6.87-7.07 (m, 4H), 7.48-7.77 (m, 3H), 7.85-7.97 (m, 2H)
IR (neat, cm^{-1}) : 2976,1752,1504, 1488, 1456, 1368, 1312, 1216, 1152, 1088, 1040, 832, 768, 688, 560. FABMS (m/z) : 125,154, 194,195,194,434,435,436 (M^++1)
HRMS : calcd. 436.159398, found 436. 162468. Melting point : 113-114°C.

<u>Part 10</u>: (2S,5S)-1-*tert*-butoxycarbonyl-2-(4-fluoro)phenoxymethyl-5-(2hydroxyethyl)ethynyl pyrrolidine (Scheme X; <u>10</u>) :

To a solution of 1-tetrahydropyranyloxy-3-butynylmagnesium bromide in THF [prepared in situ by the addition of isopropylmagnesium bromide in THF to 2-(3-butynyl-1-oxy)tetrahydropyran (0.11g, 0.7mmol)], was added a mixture of zinc bromide in THF (78mg, 0.35mmol) at ambient temperature. To the colorless suspension, formed after 30 min. of stirring, was added (5S)-2-benzenesulfonyl-1-*tert*-butoxycarbony-5-(4-fluoro) phenoxymethylpyrrolidine (0.15g, 0.35mmol) in 12 ml of THF. The reaction mixture was stirred for 10 hours. The reaction mixture was quenched with aqueous NH_4Cl solution (0.3ml) and partitioned between ether (30ml) and water (10ml). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to afford the crude product which was dissolved in methanol (1.5ml). PPTS (7mg, 0.026mmol) was added and the reaction mixture was stirred at room temperature overnight. The residue after the removal of methanol, was purified by column chromatography (60-120mesh, 30% ethyl acetate in hexane) to afford the pure product as colorless oil (100mg, 86%)
TLC: 30% ethyl acetate-hexane, $R_f = 0.4$; ^1H NMR(200 Mhz, $CDCl_3$): δ 1.49 (s, 9H), 1.55-1.82(m, 2H), 1.87-2.0(m, 1H), 2.0-2.3(m, 2H), 2.35-2.5(m, 2H), 3.6-3.75(t, 2H), 3.75-3.9(m, 1H), 3.95-4.25(m, 2H), 4.44-4.58(m, 1H), 6.77-7.0(m, 4H). FABMS(m/z) : 107, 136, 138, 154, 194, 238, 264, 308, 364 (M^++1)

Part 11: (2S,5S)-1-*tert*-butoxycarbonyl-2-(4-fluoro)phenoxymethyl-5-(4-N,O-bis-phenoxycarbonylhydroxyamino-1-butynyl)pyrrolidine (Scheme X; 11):

To a solution of (2S,5S)-1-*tert*-butoxycarbonyl-5-(2-hydroxyethyl)ethynyl-2-(4-fluoro)phenoxymethylpyrrolidine (82mg, 0.226mmol), triphenyphosphine (71mg, 0.27mmol) and N,O-bis-phenoxycarbonylhydroxylamine (70mg, 2.7mmol) was added diethyl azodicarboxylate (50mg, 0.27mmol) dropwise. The mixture was stirred for 30 min. at 0^0C and then for 6 hours at room temperature. The solvent was removed under vacuum and the residue was purified by column chromatography (30% ethyl acetate in hexane, R_f= 0.7) to afford colorless semi-solid (112mg, 80%). ^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.5 (s, 9H), 1.88-2.4 (m, 4H), 2.62-2.77 (t, 2H), 3.65-4.29 (m, 5H), 4.4-4.6 (m, 1H), 6.76-7.1 (m, 4H), 7.1-7.3 (m, 6H), 7.3-7.5 (m, 4H).

Part 12: (2S,5S)-1-*tert*-butoxycarbonyl-2-(4fluoro)phenoxymethyl-5-(4-hydroxyureidyl-1-butynyl)pyrrolidine (Scheme X; 12):

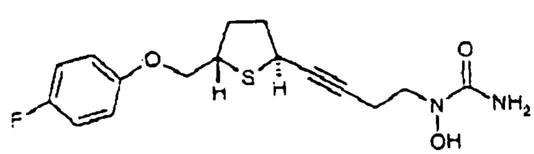
Ammonia gas was purged into a solution of (2S,5S)-1-*tert*-butoxycarbonyl-2-(4-fluoro)phenoxymethyl-5-(4-N,O-bis-phenoxycarbonylhydroxy amino-1-butynylpyrrolidine (100mg, 0.226mmol) in a solvent mixture of methanol (3ml) and THF (1 ml) at 0^0C for 15 min. The reaction mixture was stirred for 6hours at room temperature. Evaporation of the solvent and purification of the residue by column chromatography (30% ethyl acetate in hexane, R_f = 0.6) afforded 80mg of pure product as colourless liquid (85%). ^{1}H NMR (200MHz, $CDCl_3$) : δ 1.5 (s, 9H), 1.85-2.31 (m, 4H), 2.36-2.5 (t, 2H), 3.5-3.68 (m, 1H), 3.69-3.90 (m, 2H), 3.93-4.4 (dd, 1H, J= 7.9, J=3.4Hz), 4.07-4.2 (m, 1H), 4.35-4.55 (m, 1H), 5.1-5.35 (br s, 2H), 6.73-7.0 (m, 4H). IR (neat, cm^{-1}) : 3504, 3450-3000 (br), 2960, 1688, 1512, 1392, 1208,1160, 760. FABMS(m/z) : 153,194, 274, 322, 388, 422 (M^++1).

Part 13: (2S,5S) -(4-fluoro)phenoxymethyl-5-(4-hydroxyureidyl-1-butynyl)pyrrolidine (Scheme X; 13) :

Trifluoroacetic acid (0.05ml, 0.549mmol) was added to a solution of substrate (80mg, 0.183mmol) in 1ml of CH_2Cl_2 at 0^0C. The reaction mixture was stirred for 3h at room temperature. Aqueous saturated $NaHCO_3$ was added at 0^0C. After being stirred for 10 min. the organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 and concentrated to afford the brown residue which was purified by column chromatography (10% methanol in ethyl acetate $R_f = 0.6$) to afford the colourless semi-solid (55mg, 86%). ^1H NMR (200 MHz,$CDCl_3$): δ 1.5-1.97 (m, 4H), 2.01-2.25 (m, 2H), 2.38-2.6 (t, J=2.17Hz, 2H), 3.52-3.7 (t, J=6.54Hz, 2H), 3.72-4.04 (m, 4H), 6.73-7.6 (m, 4H). FABMS(m/z) : 107, 120, 124, 136, 138, 154, 176, 194, 268, 279, 322 (M^++1)

Example 4: Human whole blood assay

The following compound of the invention was tested for Leukotriene B_4 inhibition in the human whole blood assay detailed below.



Heparinized human whole blood was pre-incubated with selected concentrations of the test compound for 15 minutes at 37°C and stimulated with 50 μM calcium ionphor for 30 minutes at 37°C. The reaction was stopped by placing samples on ice and cold centrifugation at 4°C for 10 minutes at 1100 x g. Test sample plasma was diluted in buffer and assayed for LTB_4 content. Test compound activity was determined as per Cayman LTD EIA and evaluated as IC_{50} [nM]. The compound had an IC_{50} of 256 nM.

The invention has been described in detail including preferred embodiments thereof. However, it will be understood that those skilled in the art, upon consideration of this disclosure, may make modifications and improvements thereon without departing from the spirit and scope of the invention as set forth in the following claims.

What is claimed is:

1. A method for preparing a hydroxy-substituted tetrahydrothiophene, comprising:

a) providing a thioepoxy-aryl ether;

b) reacting the epoxy-aryl ether with an active methylene compound to form a lactone; and

c) reducing the lactone to provide a hydroxy-substituted tetrahydrothiophene.

2. The method of claim 1 wherein the aryl group of the thioepoxy-aryl ether is a carbocyclic aryl.

3. The method of claim 1 wherein the aryl group of the thioepoxy-aryl ether is a hetero aryl.

4. The method of claim 1 wherein the thioepoxy-aryl ether is optically active.

5. The method of claim 1 wherein the thioepoxy-aryl ether is racemic.

6. The method of claim 1 wherein the active methylene compound is a diester or a half-ester thereof.

7. The method of claim 1 wherein the active methylene compound is a dialkyl malonate.

8. The method of claim 1 further comprising activating the hydroxy group of the hydroxy-substituted tetrahydrothiophene and substituting the activated tetrahydrothiophene position.

9. The method of claim 8 wherein the tetrahydrothiophene position is substituted with a nucleophilic compound.

10. The method of claim 10 wherein the tetrahydrothiophene position is substituted with a 1-alkynyl compound.

11. The method of any one of claims 8-10 wherein the substitution produces an enantiomeric excess of a stereoisomer.

12. The method of claim 11 wherein the substitution produces a stereoisomer that is present in at least about 60 percent relative to the other stereoisomer.

13. The method of claim 11 wherein the substitution produces a stereoisomer that is present in at least about 70 percent relative to the other stereoisomer.

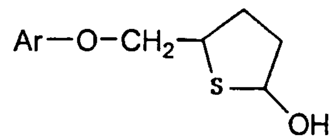
14. The method of claim 11 wherein the substitution produces a trans stereoisomer that is present in at least about 60 percent relative to the cis stereoisomer.

15. The method of claim 11 wherein the substitution produces a trans stereoisomer that is present in at least about 70 percent relative to the cis stereoisomer.

16. The method of claim 11 wherein the substitution produces a cis stereoisomer that is present in at least about 60 percent relative to the trans stereoisomer.

17. The method of claim 11 wherein the substitution produces a cis stereoisomer that is present in at least about 70 percent relative to the trans stereoisomer.

18. The method of claim of claim 1 wherein the hydroxy-substituted tetrahydrothiophene is represented by the following formula:



wherein Ar is optionally substituted carbocyclic aryl or heteroaryl.

19. The method of claim 18 wherein Ar is optionally substituted carbocyclic aryl.

20. The method of claim 18 wherein Ar is optionally substituted phenyl.

21. A method for preparing an alkynyl-substituted tetrahydrothiopene, thiane, thiepane, or thiocane, comprising:

treating with base a compound comprising a substituted alkyl group to form an alkynyl-substituted tetrahydrothiopene, alkynyl-substituted thiane, alkynyl-substituted thiepane, or alkynyl-substituted thiocane,

wherein the substituted alkyl group has 6, 7, 8, 9 or more carbon atoms, the 2,3-positions of alkyl group forming an epoxide ring, the 1-position of the alkyl group substituted with a first leaving group, and the 6-,7-, 8- or 9-position of the alkyl group substituted with a second leaving group.

22. The method of claim 21 wherein the substituted alkyl compound is treated with a molar excess of base.

22. The method of claim 21 wherein the substituted alkyl compound is treated with about a three molar excess of base.

23. The method of claim 21 wherein the base is an alkyllithium reagent, an amide salt or a hydride.

24. The method of claim 21 wherein the first and second leaving groups are each independently a halogen, a sulfonic alkyl ester, a sulfonic aryl ester or a sulfonic arylalkyl ester.

25. The method of claim 21 wherein one or both of the epoxide carbons are optically active.

26. The method of claim 21 wherein the formed tetrahydrothiopene, thiane, thiepane, or thiocane is optically active.

27. The method of claim 21 wherein both of the epoxide carbons are optically active.

28. The method of claim 27 wherein the two carbons adjacent to the ring sulfur of the formed tetrahydrothiopene, thiane, thiepane, or thiocane are each optically active.

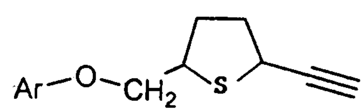
29. The method of claim 27 wherein the tetrahydrothiopene, thiane, thiepane, or thiocane is formed from the substituted alkyl compound without isolation of intermediate compounds.

30. The method of claim 29 wherein the tetrahydrothiopene, thiane, thiepane, or thiocane is formed from the substituted alkyl compound in a single reaction step.

31. The method of claim 21 wherein the substituted alkyl compound is substituted at the 7, 8 or 9 carbons by an alkoxy, arylalkoxy or aryloxy group.

32. The method of claim 21 where the alkyl-substituted compound is substituted at the 6-position with the second leaving group, and treatment with base provides an alkynyl-substituted tetrahydrothiophene.

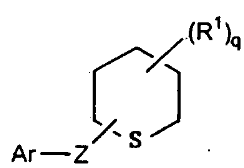
33. The method of claim 32 wherein a tetrahydrothiophene of the following formula is provided:



wherein Ar is optionally substituted carbocyclic aryl or heteroaryl.

34. The method of claim 21 where the alkyl-substituted compound is substituted at the 7-position with the second leaving group, and treatment with base provides an alkynyl-substituted thiane.

35. The method of claim 34 where the thiane is represented by the following formula:



wherein Ar is optionally substituted carbocyclic aryl or heteroaryl;

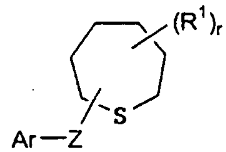
Z is a chemical bond, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, or a hetero atom;

each R^1 is independently hydrogen or a non-hydrogen substituent, at least one R^1 being present as a 1-alkynyl substituted on the thiane ring;.

q is an integer of from 1 to 9.

36. The method of claim 21 where the alkyl-substituted compound is substituted at the 8-position with the second leaving group, and treatment with base provides an alkynyl-substituted thiepane.

37. The method of claim 36 where the thiepane is represented by the following formula:



wherein Ar is optionally substituted carbocyclic aryl or heteroaryl;

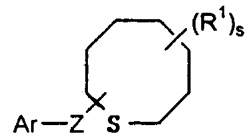
Z is a chemical bond, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, or a hetero atom;

each R^1 is independently hydrogen or a non-hydrogen substituent, at least one R^1 being present as a 1-alkynyl substituted on the thiepane ring;.

r is an integer of from 1 to 9.

38. The method of claim 21 where the alkyl-substituted compound is substituted at the 9-position with the second leaving group, and treatment with base provides an alkynyl-substituted thiocane.

39. The method of claim 38 where the thiocane is represented by the following formula:



wherein Ar is optionally substituted carbocyclic aryl or heteroaryl;

Z is a chemical bond, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, or a hetero atom;

each R^1 is independently hydrogen or a non-hydrogen substituent, at least one R^1 being present as a 1-alkynyl substituted on the thiocane ring;.

s is an integer of from 1 to 11.

40. A method for preparing an alkynyl-substituted pyrrolidine, hexahydropyridine, hexahydroazepine or octahydroazocine, comprising:

treating with base a compound comprising a substituted alkyl group to form an alkynyl-substituted pyrrolidine, alkynyl-substituted hexahydropyridine , alkynyl-substituted hexahydroazepine, or alkynyl-substituted octahydroazocine,

wherein the substituted alkyl group has 6, 7, 8, 9 or more carbon atoms, the 2,3-positions of alkyl group forming an epoxide ring, the 1-position of the alkyl group substituted with a leaving group, and the 6-,7-, 8- or 9-position of the alkyl group substituted with an azido group.

41. The method of claim 40 wherein the substituted alkyl compound is treated with a molar excess of base.

42. The method of claim 40 wherein the substituted alkyl compound is treated with about a three molar excess of base.

43. The method of claim 40 wherein the base is an alkyllithium reagent, an amide salt or a hydride.

44. The method of claim 40 wherein the leaving group is halogen, a sulfonic alkyl ester, a sulfonic aryl ester or a sulfonic arylalkyl ester.

45. The method of claim 40 wherein one or both of the epoxide carbons are optically active.

46. The method of claim 40 wherein the formed pyrrolidine, hexahydropyridine, hexahydroazepine or octahydroazocine is optically active.

47. The method of claim 40 wherein both of the epoxide carbons are optically active.

48. The method of claim 40 wherein the two carbons adjacent to the ring nitrogen of the formed pyrrolidine, hexahydropyridine, hexahydroazepine or octahydroazocine are each optically active.

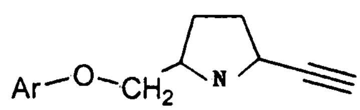
49. The method of claim 40 wherein the pyrrolidine, hexahydropyridine, hexahydroazepine or octahydroazocine is formed from the substituted alkyl compound without isolation of intermediate compounds.

50. The method of claim 40 wherein the pyrrolidine, hexahydropyridine, hexahydroazepine or octahydroazocine is formed from the substituted alkyl compound in a single reaction step.

51. The method of claim 40 wherein the substituted alkyl compound is substituted at the 7, 8 or 9 carbons by an alkoxy, arylalkoxy or aryloxy group.

52. The method of claim 40 where the alkyl-substituted compound is substituted at the 6-position with the azido group, and treatment with base provides an alkynyl-substituted pyrrolidine.

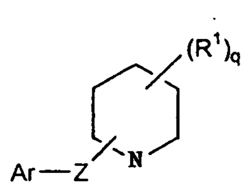
53. The method of claim 52 wherein a pyrrolidine of the following formula is provided:



wherein Ar is optionally substituted carbocyclic aryl or heteroaryl.

54. The method of claim 40 where the alkyl-substituted compound is substituted at the 7-position with the azido leaving group, and treatment with base provides an alkynyl-substituted hexahydropyridine.

55. The method of claim 54 where the hexahydropyridine is represented by the following formula:



wherein Ar is optionally substituted carbocyclic aryl or heteroaryl;

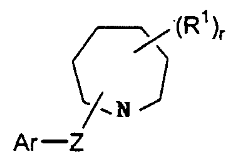
Z is a chemical bond, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, or a hetero atom;

each R^1 is independently hydrogen or a non-hydrogen substituent, at least one R^1 being present as a 1-alkynyl substituted on the hexahydropyridine ring;.

q is an integer of from 1 to 9.

56. The method of claim 40 where the alkyl-substituted compound is substituted at the 8-position with the azido group, and treatment with base provides an alkynyl-substituted hexahydroazepine.

57. The method of claim 56 where the hexahydroazepine is represented by the following formula:



wherein Ar is optionally substituted carbocyclic aryl or heteroaryl;

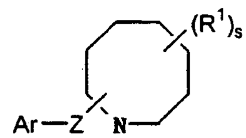
Z is a chemical bond, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, or a hetero atom;

each R^1 is independently hydrogen or a non-hydrogen substituent, at least one R^1 being present as a 1-alkynyl substituted on the hexahydroazepine ring;.

r is an integer of from 1 to 9.

58. The method of claim 40 where the alkyl-substituted compound is substituted at the 9-position with the azido group, and treatment with base provides an alkynyl-substituted octahydroazocine.

59. The method of claim 58 where the octahydroazocine is represented by the following formula:



wherein Ar is optionally substituted carbocyclic aryl or heteroaryl;

Z is a chemical bond, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, or a hetero atom;

each R^1 is independently hydrogen or a non-hydrogen substituent, at least one R^1 being present as a 1-alkynyl substituted on the octahydroazocine ring;.

s is an integer of from 1 to 11.

60. A method for preparing an N-hydroxy-substituted urea compound, comprising

(a) reacting a urea compound where at least one of the urea nitrogens is protected with a methoxybenzyl group,

(b) in the presence of a dehydrating agent, reacting the protected urea an alkyl or aryl group that comprises a hydroxy substituent,

(c) treating the compound of step (b) with ammonia and a Lewis acid.

61. The method of claim 60 wherein the dehydrating agent is a triphenyl phosphine and diethylazodicarboxylate.

62. The method of claim 60 wherein the protecting group is para-methoxybenzyl.

63. The method of claim 60 wherein the Lewis acid is boron trifluoride.

64. A method for preparing an aryl-substituted alicyclic compound having a nitrogen ring member, comprising:

reacting an alicyclic compound having a nitrogen ring member and an alkyl ring substituent with an aryl nucleophile in the presence of a hydride reagent to yield the alicyclic compound having an arylalkyl substituent.

65. The method of claim 64 wherein the aryl nucleophile is an aryl hydroxy compound and the reaction yields an alicyclic compound having an aryloxyalkyl substituent.

66. The method of claim 64 or 65 wherein the aryl nucleophile is a carbocyclic aromatic compound.

67. The method of claim 66 wherein the aryl nucleophile is an optionally substituted phenol.

68. The method of claim 64 wherein alkyl ring substituent is a substituted methyl group.

69. The method of claim 64 wherein the alicyclic compound is a pyrrolidine, hexahydropyridine, hexahydroazepine or octahydroazocine compound.

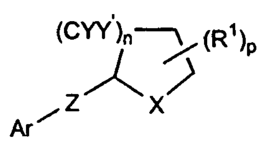
70. A method for preparing a substituted alicyclic compound having a nitrogen ring member, comprising:

reacting an alicyclic compound having a nitrogen ring member and an alkoxy ring substituent with a sulfinic acid reagent to form a sulfonyl ring substituent.

71. The method of claim 70 wherein the alicyclic compound with sulfinic substituent is reacted with an alkynyl compound to yield an alicyclic compound having an alkynyl ring substituent.

72. The method of claim 70 wherein the an optionally substituted phenylsulfinic reagent is reacted with the alicyclic compound.

73. A compound of the following Formula I:



I

wherein X is S, S(O), $S(O)_2$, N or substituted N (including N-alkyl and N-oxide);

Ar is optionally substituted carbocyclic aryl or optionally substituted heteroaryl;

each R^1, Y and Y' is independently hydrogen or a non-hydrogen substituent;

Z is a chemical bond, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, or a hetero atom such as O, S, S(O), $S(O)_2$, or NR^1 wherein R^1 is the same as defined immediately above;

n is an integer from 2 to 11;

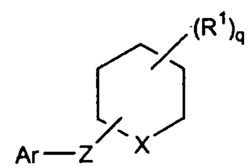
p is an integer from 0; and pharmaceutically acceptable salts thereof.

74. A compound of claim 73 wherein n is 1.

75. A compound of claim 73 wherein X is optionally substituted nitrogen or sulfur.

76. A compound of claim 73 wherein each R^1, Y and Y' is independently hydrogen, as halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl preferably, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkylthio, optionally substituted alkylsulfinyl, optionally substituted alkylsulfonyl, optionally substituted aminoalkyl, optionally substituted alkanoyl, optionally substituted carbocyclic aryl having at least about 6 ring carbons, or substituted or unsubstituted aralkyl having at least about 6 ring carbons.

77. A compound of the following Formula III:



III

wherein X is S, S(O), $S(O)_2$, N or substituted N;

Ar is optionally substituted carbocyclic aryl or optionally substituted heteroaryl;

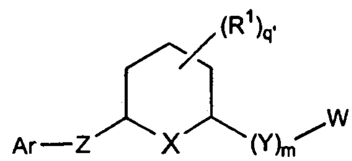
each R^1 is independently hydrogen or a non-hydrogen substituent;

Z is a chemical bond, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, or a

hetero atom such as O, S, S(O), $S(O)_2$, or NR^1 wherein R^1 is the same as defined immediately above;

and q is an integer of from 0 to 9, and pharmaceutically acceptable salts thereof.

78. A compound of claim 77 wherein the compound is of the following Formula IIIa:



IIIa

wherein Ar, X, Z, R^1 and q' are the same as defined for Formula III;

W is $-AN(OM)C(O)N(R^3)R^4$, $-N(OM)C(O)N(R^3)R^4$, $-AN(R^3)C(O)N(OM)R^4$, $-N(R^3)C(O)N(OM)R^4$, $-AN(OM)C(O)R^4$, $-N(OM)C(O)R^4$, $-AC(O)N(OM)R^4$, $-C(O)N(OM)R^4$, or –C(O)NHA; and A is lower alkyl, lower alkenyl, lower alkynyl, alkylaryl or arylalkyl, wherein one or more carbons optionally can be replaced by N, O or S, however -Y-A-, -A-, or -AW- should not include two adjacent heteroatoms;

M is hydrogen, a pharmaceutically acceptable cation or a metabolically cleavable leaving group;

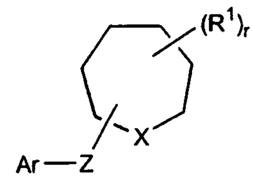
Y is O, S, S(O), $S(O)_2$, NR^3 or CHR^5;

R^3 and R^4 are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, C_{1-6}alkoxy-C_{1-10}alkyl, C_{1-6} alkylthio-C_{1-10} alkyl, heteroaryl, or heteroarylalkyl;

R^5 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, arylalkyl, alkaryl, $-AN(OM)C(O)N(R^3)R^4$, $-AN(R^3)C(O)N(OM)R^4$, $-AN(OM)C(O)R^4$, $-AC(O)N(OM)R^4$, $-AS(O)_xR^3$, $-AS(O)_xCH_2C(O)R^3$, $-AS(O)_xCH_2CH(OH)R^3$, or $-AC(O)NHR^3$, x is 0, 1 or 2;

m is 0 or 1; and pharmaceutically acceptable salts thereof.

79. A compound of the following Formula IV:



IV

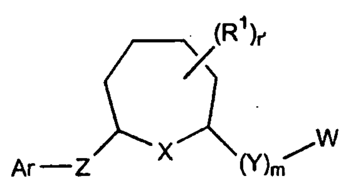
wherein X is S, S(O), $S(O)_2$, N or substituted N;

Ar is optionally substituted carbocyclic aryl or optionally substituted heteroaryl;

each R^1 is independently hydrogen or a non-hydrogen substituent;

Z is a chemical bond, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, or a hetero atom such as O, S, S(O), $S(O)_2$, or NR^1 wherein R^1 is the same as defined immediately above; and r is an integer of from 0 to 11; and pharmaceutically acceptable salts thereof.

80. A compound of claim 79 wherein the compound is of the Formula Formula IVa:



IVa

wherein Ar, Z, X, and R^1 are the same as defined for Formula IV above;

W is -AN(OM)C(O)N(R^3)R^4, -N(OM)C(O)N(R^3)R^4, -AN(R^3)C(O)N(OM)R^4, -N(R^3)C(O)N(OM)R^4, -AN(OM)C(O)R^4, -N(OM)C(O)R^4, -AC(O)N(OM)R^4, -C(O)N(OM)R^4, or –C(O)NHA; and A is lower alkyl, lower alkenyl, lower alkynyl, alkylaryl or arylalkyl, wherein one or more carbons optionally can be replaced by N, O or S, however -Y-A-, -A-, or -AW- should not include two adjacent heteroatoms;

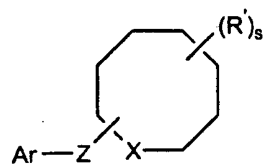
M is hydrogen, a pharmaceutically acceptable cation or a metabolically cleavable leaving group;

Y is O, S, S(O), $S(O)_2$, NR^3 or CHR^5;

R^3 and R^4 are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, C_{1-6}alkoxy-C_{1-10}alkyl, C_{1-6} alkylthio-C_{1-10} alkyl, heteroaryl, or heteroarylalkyl;

R^5 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, arylalkyl, alkaryl, -AN(OM)C(O)N(R^3)R^4, -AN(R^3)C(O)N(OM)R^4, -AN(OM)C(O)R^4, -AC(O)N(OM)R^4, -AS(O)$_x$$R^3$, -AS(O)$_x$$CH_2$C(O)$R^3$, -AS(O)$_x$$CH_2$CH(OH)$R^3$, or –AC(O)NH$R^3$, x is 0, 1 or 2; and r' is an integer of from 0 to 10; and pharmaceutically acceptable salts thereof.

81. A compound of the following Formula V:



V

wherein X is S, S(O), $S(O)_2$, N or substituted N;

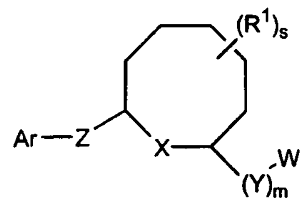
Ar is optionally substituted carbocyclic aryl or optionally substituted heteroaryl;

each R^1 is independently hydrogen or a non-hydrogen substituent;

Z is a chemical bond, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, or a hetero atom such as O, S, S(O), $S(O)_2$, or NR^1 wherein R^1 is the same as defined immediately above;

and s is an integer of from 0 to 13; and pharmaceutically acceptable salts thereof.

82. A compound of claim 81 wherein the compound is of the following Formula Va:



Va

wherein Ar, X, Z, and R^1 are each the same as defined for Formula V;

W is $-AN(OM)C(O)N(R^3)R^4$, $-N(OM)C(O)N(R^3)R^4$, $-AN(R^3)C(O)N(OM)R^4$, $-N(R^3)C(O)N(OM)R^4$, $-AN(OM)C(O)R^4$, $-N(OM)C(O)R^4$, $-AC(O)N(OM)R^4$, $-C(O)N(OM)R^4$, or $-C(O)NHA$; and A is lower alkyl, lower alkenyl, lower alkynyl, alkylaryl or arylalkyl, wherein one or more carbons optionally can be replaced by N, O or S, however -Y-A-, -A-, or -AW- should not include two adjacent heteroatoms;

M is hydrogen, a pharmaceutically acceptable cation or a metabolically cleavable leaving group;

Y is O, S, S(O), $S(O)_2$, NR^3 or CHR^5;

R^3 and R^4 are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, C_{1-6}alkoxy-C_{1-10}alkyl, C_{1-6} alkylthio-C_{1-10} alkyl, heteroaryl, or heteroarylalkyl;

R^5 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, arylalkyl, alkaryl, $-AN(OM)C(O)N(R^3)R^4$, $-AN(R^3)C(O)N(OM)R^4$, $-AN(OM)C(O)R^4$, $-AC(O)N(OM)R^4$, $-AS(O)_xR^3$, $-AS(O)_xCH_2C(O)R^3$, $-AS(O)_xCH_2CH(OH)R^3$, or $-AC(O)NHR^3$, x is 0, 1 or 2;

and s is an integer of from 0 to 10; and pharmaceutically acceptable salts thereof.

83. A pharmaceutical composition comprising a compound of any one of claims 73-82 and a pharmaceutically acceptable carrier.

84. A method of treating a disorder or disease associated with 5-lipoxygenase, comprising administering to a subject suffering from or susceptible to such a disease or disorder an effective amount of a compound or composition of any one of claims 73-83.

85. A method of treating a immune, allergic or cardiovascular disorder or disease, comprising administering to a subject suffering from or susceptible to such a disease or disorder an effective amount of a compound of any one of claims 73-83.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/15050

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/236; 548/551, 552, 556, 570; 549/13, 62, 78; 514/317, 424, 428, 431, 432, 445

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,543,531 A (FUNFSCHILLING) 06 August 1996, see the entire document.	1-20,73-85
A	US 5,756,768 A (KANOU et al) 26 May 1998, see the entire document.	1-20,73-85

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

26 SEPTEMBER 1999

Date of mailing of the international search report

03 NOV 1999

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Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/15050

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-20,73-85

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/15050

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07D 207/08, 211/20, 333/16, 333/32, 335/02; A61K 31/38,31/40, 31/445

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

546/236; 548/551, 552, 556, 570; 549/13, 62, 78; 514/317, 424, 428, 431, 432, 445

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

1.Group 1, claims 1-20, drawn to a method for preparing a hydroxy-substituted tetrahydrothiophene using a lactone as an intermediate.
2.Group 2, claims 21-32 and claim 33, drawn to a method for preparing an alkynyl-substituted tetrahydrothiophene.

3.Group 3, claims 21-32 and claims 34-35, drawn to a method for preparing an alkynyl-substituted thiane.
4. Group 4, claims 21-32 and claims 36-37, drawn to a method for preparing an alkynyl-substituted thiepane.
5. Group 5, claims 21-32 and claims 38-39, drawn to a method for preparing an alkynyl-substituted thiocane.
6. Group 6, claims 40-51 and claims 52-53, drawn to a method for preparing an alkynyl-substituted pyrrolidine.
7. Group 7, claims 40-51 and claims 54-55, drawn to a method for preparing an alkynyl-substituted hexahydropyridine.
8. Group 8, claims 40-51 and claims 56-57, drawn to a method for preparing an alkynyl-substituted hexahydroazepine.
9. Group 9, claims 40-51 and claims 58-59, drawn to a method for preparing an alkynyl-substituted octahydroazocine.
10. Group 10, claims 60-63, drawn to a method for preparing an N-hydroxy-substituted urea compound.
11. Group 11, claims 64-69, drawn to a method for preparing an aryl-substituted alicyclic compound having a nitrogen ring member.
12. Group 12, claims 70-72, drawn to a method for preparing a substitued alicyclic compound using a sulfur-containing reagent as an intermediate.
13. Group 13, claims 73-76, 83-85 and claims 77-78, drawn to a 6-member heterocyclic compound,its composition and methods of uses.
14. Group 14, claims 73-76, 83-85 and claims 79-80, drawn to a 7-member heterocyclic compound,its composition and methods of uses.
15. Group 15, claims 73-76, 83-85 and claims 81-82, drawn to a 8-member heterocyclic compound,its composition and methods of uses.

The inventions listed as Groups 1-15 do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The aboved delineated groups are distinct because each group involves different reaction reagents and conditions,and the products made by each group are also distinct because of their recognized divergent subject matter as shown by their different chemical structures,different ring size,ring member and substituents.